Review

Mechanisms of Bifidobacterium as an Adjuvant Therapy for Improving Sleep Quality and Neuroendocrine Regulation in Bipolar Disorder: A Narrative Review

Chunmei Li[1]
Xue Li[2,3,*]

[1]Department of Pharmacy, West China Hospital, Sichuan University, 610041 Chengdu, Sichuan, China
[2]Department of Pediatrics, West China Second University Hospital, Sichuan University, 610041 Chengdu, Sichuan, China
[3]Key Laboratory of Birth Defects and Related Diseases of Women and Children, Sichuan University, Ministry of Education, 610041 Chengdu, Sichuan, China

Abstract

Bifidobacterium, a genus of beneficial gut bacteria, is widely recognised for regulating gut microbiota homeostasis, modulating immune function, and maintaining metabolic balance. Modern research suggests that it exerts regulatory effects on the gut–brain axis, thereby influencing central nervous system function and improving mental health outcomes. It may regulate neurotransmitters by promoting serotonin precursor synthesis and balancing dopamine release. It could restore the negative feedback of the hypothalamic–pituitary–adrenal axis and optimise the function of the hypothalamic–pituitary–thyroid axis. Additionally, it may suppress inflammatory cytokines, regulate tryptophan metabolism, and maintain immune cell homeostasis. Regarding sleep improvement, it might act by regulating circadian clock genes and gut–brain axis-mediated central inhibitory pathways. Preliminary clinical evidence shows that its combination with conventional treatments may enhance sleep efficiency and mood in patients with depression, with good safety profiles. Despite the lack of large-scale studies evaluating the application of Bifidobacterium in bipolar disorder (BD), and the fact that no sufficient scientific evidence currently supports its direct treatment of BD, its multi-system regulatory properties align closely with the pathological mechanisms of BD, suggesting its potential as a novel option for the comprehensive management of BD-related sleep disturbances and hormone imbalances.

Keywords

bipolar disorder; Bifidobacterium; sleep quality; neuroendocrine; inflammatory-immune; gut–brain axis

Introduction

Bipolar disorder (BD) is a chronic, recurrent severe mental disorder marked by episodic mania/hypomania and depression, with sleep disturbances and neuroendocrine dysregulation as core and interrelated clinical features that contribute to disease progression and poor prognosis. Current first-line pharmacotherapies for BD have limitations including narrow therapeutic windows, severe adverse effects, and inadequate improvement in sleep disturbances and neuroendocrine dysfunction, highlighting an unmet need for safe and effective adjuvant interventions. The gut–brain axis (GBA) has emerged as a pivotal regulatory pathway linking gut microbiota homeostasis to central nervous system (CNS) function, neuroendocrine regulation, and immune activity—key pathological processes in BD. Specific strains of Bifidobacterium, a dominant commensal gut bacterium, exert multi-system regulatory effects by modulating GBA signalling, including neurotransmitter synthesis, neuroendocrine axis function, and inflammatory-immune balance. Accumulating preclinical evidence supports their potential to improve sleep quality and regulate neuroendocrine

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*Corresponding author details: Xue Li, Department of Pediatrics, West China Second University Hospital, Sichuan University, 610041 Chengdu, Sichuan, China; Key Laboratory of Birth Defects and Related Diseases of Women and Children, Sichuan University, Ministry of Education, 610041 Chengdu, Sichuan, China. Email: xiaoxuelee@yeah.net

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function, yet their mechanistic role and clinical value as an adjuvant therapy for BD remain poorly characterised and have not been validated in large-scale clinical studies.

This review elucidates the potential mechanisms by which specific strains of Bifidobacterium modulate sleep and neuroendocrine function in BD through the GBA, analyses its potential synergistic effects with conventional medical treatments, and discusses its safety, administration guidelines, and future research directions. The aim is to provide a theoretical basis for the development of gut microbiota-targeted adjuvant therapies for BD and to expand the comprehensive management strategy for this mental disorder. This review advances existing literature on GBA and probiotic interventions in mental disorders by focusing on BD, an understudied population in microbiota research, and synthesising strain-specific mechanistic links between Bifidobacterium, sleep regulation, and neuroendocrine dysfunction.

Epidemiological Characteristics of BD and Associated Sleep Disturbances

BD is a complex and severe mental disorder characterised by alternating episodes of mania or hypomania and depression [1]. Globally, BD affects a substantial number of people, imposing a heavy burden on patients, their families, and society. According to the World Health Organization (WHO), the global prevalence of BD is approximately 0.5% [2], which varies slightly across different regions and studies. For instance, in Europe and America, the lifetime prevalence can reach 3%–4%, whereas in Asia, although relatively lower, it remains significant. A large-scale epidemiological survey in China showed that the weighted lifetime prevalence of BD is 0.6% and the annual weighted prevalence is 0.5% [3].

The clinical manifestations of BD are complex. During manic episodes, patients may experience elevated mood, flight of ideas, increased activity, reduced sleep needs, inflated self-esteem, irritability, and in severe cases, may present with psychotic symptoms such as hallucinations and delusions [4]. In depressive episodes, symptoms include low mood, loss of interest, anhedonia, fatigue, slowed thinking, self-reproach, sleep disturbances, changes in appetite, suicidal ideation, or behaviour [5]. These symptoms not only severely impact patients' daily lives, work, study, and social relationships but also significantly increase the risk of suicide. The suicide rate among patients with BD is several times higher than that in the general population. Approximately 15%–25% of patients with BD have attempted suicide, and 5%–15% ultimately die by suicide [6].

Sleep disturbances are one of the most common accompanying symptoms in patients with BD, persisting throughout all stages of the disease and severely affecting patients' quality of life, disease prognosis, and recurrence risk [7]. During depressive episodes, patients often experience insomnia symptoms such as difficulty falling asleep, early morning awakening, poor sleep maintenance, and decreased sleep quality. Some patients may also experience hypersomnia. In manic or hypomanic episodes, patients exhibit reduced sleep needs, with abundant energy and no sense of fatigue despite substantially shortened sleep time [8]. Studies have shown that about 70%–90% of patients with BD suffer from various forms of sleep disturbances [9,10]. Sleep disturbances are not only a symptom of BD but also closely related to the onset, severity, and recurrence of the disease. Insomnia often serves as a prodromal symptom of manic or depressive episodes in patients with BD, increasing the risk of episodes, prolonging their duration, and exacerbating symptom severity [10]. Good sleep helps stabilise the mood of patients with BD, improves cognitive function, and may enhance treatment compliance. Conversely, sleep deprivation or disorders may trigger or worsen the condition, creating a vicious cycle.

Pathogenesis of BD

BD has a significant genetic predisposition, with genetic factors playing a key role in its pathogenesis [11]. Genome-wide association studies (GWAS) have identified susceptibility genes such as *ANK3*, *CACNA1C*, and *BDNF*. Among these, *ANK3* increases the risk of BD by affecting neuronal plasticity [12]. However, BD is not a single-gene disease; rather, it results from the interaction between multiple genes and the environment, with considerable ethnic heterogeneity. For example, TMEM108 has been reported to be associated with BD in the Han Chinese population, but this association has not been validated in the European populations [13].

During manic episodes, there is hyperactivity of dopamine (DA) function in the ventral tegmental area and prefrontal cortex, leading to excitement and impulsivity. In depressive episodes, reduced dopaminergic activity may cause anhedonia [10]. Antipsychotic medications control manic symptoms by blocking DA receptors [14]. In patients with BD, the metabolites of 5-hydroxytryptamine (5-HT) in cerebrospinal fluid (CSF) are decreased, and the function of 5-HT receptors is abnormal. Selective serotonin reuptake inhibitors (SSRIs) improve depressive symptoms by enhancing 5-HT transmission [15]. Norepinephrine (NE) lev-

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els decrease during depressive episodes and may increase during manic episodes, and NE reuptake inhibitors are effective in treating BD [16].

During depressive episodes, cortisol levels increase, and the dexamethasone suppression test is abnormal. Prolonged high cortisol levels damage neural plasticity [17]. The mechanism of hypothalamic–pituitary–adrenal (HPA) axis rhythm disorder during manic episodes remains unclear. Abnormal thyroid function is associated with BD symptoms. Hypothyroidism exacerbates depression, while hyperthyroidism may trigger mania. Modulating the hypothalamic–pituitary–thyroid (HPT) axis can serve as an adjuvant treatment [18].

In patients with BD, levels of inflammatory cytokines such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α) are elevated. These cytokines participate in the pathogenesis by interfering with tryptophan metabolism (reducing 5-HT synthesis), disrupting the blood-brain barrier, and damaging nerve cells. Imbalances in the functions of T and B cells may also contribute to the disease [19].

The occurrence mechanism of sleep disturbances in patients with BD is closely related to neurotransmitter imbalances, neuroendocrine disorders, circadian rhythm disruptions, and psychological factors. Imbalances in neurotransmitters such as DA, 5-HT, and NE are involved in the pathogenesis of both BD and sleep disturbances. Dysfunction of the HPA axis leads to abnormal cortisol secretion, interfering with the normal sleep–wake cycle. Abnormal expression of circadian clock genes such as PER and CRY disrupts the body's circadian rhythm, thereby affecting sleep [20]. Consequently, patients with BD often experience emotional issues such as anxiety and depression, which further exacerbate sleep disturbances. Notably, emerging evidence suggests that gut microbiota dysbiosis, including alterations in the abundance of specific Bifidobacterium strains, may be involved in these pathological processes by regulating the GBA.

Current Treatment of BD

Current treatment for BD mainly involves comprehensive interventions including pharmacotherapy, psychotherapy, and physical therapy. Pharmacotherapy serves as the foundation, with commonly used medications including mood stabilisers (such as lithium salts, valproates, carbamazepine), antipsychotics (such as olanzapine, quetiapine, aripiprazole), and antidepressants (used cautiously under specific circumstances) [21]. As a classic mood stabiliser, lithium is effective in preventing BD recurrence and controlling manic and depressive symptoms. However, lithium has a narrow therapeutic window, is associated with numerous adverse reactions, and is ineffective in some patients [22]. Antipsychotics, especially atypical antipsychotics, are widely used in controlling manic symptoms and improving sleep, but they also have side effects such as weight gain and metabolic disorders [23]. Antidepressants used alone may trigger manic episodes and are usually prescribed in combination with mood stabilisers, with careful consideration of the timing and dosage.

Although existing treatment methods can relieve symptoms in some patients with BD, a considerable proportion of patients still have unsatisfactory treatment outcomes, including residual symptoms, high recurrence rates, and severe adverse reactions. Approximately 30%–40% of patients with BD do not respond well to first-line pharmacological treatments and are classified as having treatment-resistant BD [24]. Meanwhile, the adverse effects of long-term use of psychiatric medications, such as weight gain, metabolic syndrome, and increased cardiovascular risks, severely affect patients' quality of life and treatment compliance. Therefore, finding safe and effective adjuvant treatment to improve sleep quality, regulate neuroendocrine function, and may enhance the overall treatment outcome of patients with BD has become an important topic in the current research field of BD. In this context, gut microbiota-targeted interventions, particularly those involving specific strains of Bifidobacterium, have attracted increasing attention due to their favourable safety profiles and multi-system regulatory potential, though their role is limited to adjuvant support rather than direct treatment. Notably, some probiotic intervention studies in mental disorders have reported no effects on sleep and neuroendocrine markers [25].

Application and Potential Mechanisms of Bifidobacterium in the Treatment of Mental Disorders

This section is structured under a clinically oriented framework to enhance translational readability, with clear classification of clinical application value, preclinical evidence support, clinical translational limitations, and evidence grading for each mechanism, aiming to provide clear reference for clinical practice.

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Clinical Relevance & Biological Characteristics of Bifidobacterium

The GBA, a bidirectional communication network involving neural, endocrine, immune, and metabolic pathways, plays a crucial role in regulating CNS function and emotional behaviour [26]. Specific strains of Bifidobacterium, a key genus of beneficial bacteria in the human gut, are widely distributed in the colon and small intestine, with high abundance in healthy individuals, especially infants. Key strains with demonstrated neuroregulatory effects include *Bifidobacterium longum* (strains 1714, BB536), *Bifidobacterium infantis* (35624), and *Bifidobacterium lactis* (BB-12), each exhibiting distinct functional profiles in gut barrier protection and metabolite production [27]. These strains exhibit strong acid and bile resistance, enabling them to colonise the intestinal tract and exert long-term biological effects [27].

Functionally, specific Bifidobacterium strains maintain gut microbiota homeostasis by competing with pathogenic bacteria for nutrients and adhesion sites, inhibiting the growth of harmful microorganisms such as *Escherichia coli* and *Clostridium difficile* [28]. They also promote the synthesis of intestinal tight junction proteins (e.g., occludin, zonula occludens-1), enhancing gut barrier integrity and reducing the translocation of lipopolysaccharides and other pro-inflammatory substances into the bloodstream [29]. Additionally, specific Bifidobacterium strains produce a variety of bioactive metabolites, including short-chain fatty acids (SCFAs, e.g., butyrate, propionate), B vitamins, and neurotransmitter precursors (e.g., tryptophan), which serve as key messengers in gut–brain communication [30]. These biological characteristics lay the foundation for specific Bifidobacterium strains to potentially regulate mental health, particularly in improving sleep quality and balancing neurotransmitter levels—two core unmet needs in BD management.

Clinical Relevance: Neurotransmitter Regulation in BD Pathophysiology

Clinical Relevance: Modulation of the Serotonergic System for Depressive & Sleep Symptoms

Specific Bifidobacterium strains may enhance 5-HT synthesis and NF-κB signalling through multiple pathways, addressing the 5-HT deficiency observed in BD depressive episodes [31]. First, *Bifidobacterium longum* (1714, BB536) and *Bifidobacterium infantis* (35624) may upregulate the expression of tryptophan hydroxylase-1 (TPH-1) in intestinal epithelial cells, accelerating the conversion of dietary tryptophan to 5-hydroxytryptophan (5-HTP)—the direct precursor of 5-HT [32,33]. Intestinal-derived 5-HTP, unlike peripheral 5-HT, may cross the blood–brain barrier (BBB) when neuroinflammation is reduced; peripheral 5-HT itself cannot penetrate the BBB [34]. Once in the CNS, 5-HTP is converted to 5-HT in the raphe nucleus, potentially supporting central serotonergic signalling. In a mouse model of depressive, supplementation with *Bifidobacterium longum* 1714 increased hippocampal 5-HT levels by 28% (measured via high-performance liquid chromatography; 4 weeks of oral gavage at 1×10^9 CFU/day), accompanied by improved sleep latency [35]. Second, SCFAs produced by bifidobacteria (notably butyrate) suppress monoamine oxidase (MAO) activity. Mechanistically, brain-delivered SCFAs activate ACSS2 to drive neuronal TPH2 upregulation via the PPARγ axis, enhancing central 5-HT synthesis and hippocampal 5-HT availability [36]. Notably, this regulation is not likely to be excessive, potentially avoiding the risk of 5-HT overactivation that may trigger manic episodes, which aligns with the need for balanced neurotransmitter modulation in BD. Evidence for this effect is limited to rodent models, and no human studies in BD have yet validate these findings.

Clinical Relevance: Dopaminergic Homeostasis for Manic Episode Control

In response to DA hyperactivity in BD manic episodes, *Bifidobacterium infantis* 35624 may exert region-specific regulatory effects on the DA system, though these mechanisms remain speculative and based solely on rodent model data [37,38]. Gastric-derived metabolites of *Bifidobacterium infantis* 35624 (e.g., indole-3-lactic acid) may inhibit the phosphorylation of dopamine transporter (DAT) in the ventral tegmental area, reducing presynaptic DA reuptake and indirectly lowering DA concentrations in the nucleus accumbens—a key brain region associated with reward and impulsivity [37]. In the maternal separation model of depression in rats, chronic *Bifidobacterium infantis* 35624 administration (1×10^{10} CFU/day in drinking water for 2 weeks) reduced dopamine metabolite (DOPAC) concentrations in the amygdaloid cortex and normalized brainstem noradrenaline levels, supporting its modulatory role in central monoamine pathways [38]. Additionally, *Bifidobacterium longum* BB536 may enhance the sensitivity of D2 autoreceptors in the prefrontal cortex, potentially strengthening the negative feedback regulation of dopaminergic neurons and preventing excessive DA release [39]. No clinical evidence currently supports DA modulation by Bifidobacterium in BD, and these effects have not been confirmed in human studies.

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Clinical Relevance: Noradrenergic Stabilisation for Stress-Related Mood Instability

Chronic stress-induced noradrenergic dysregulation contributes to mood instability and sleep fragmentation in BD. Specific Bifidobacterium strains (*B. lactis* BB-12, *B. longum* 1714) may stabilise the NE system through three mechanisms, all demonstrated in preclinical rodent models with no translational human data: (1) promoting the remodelling of dendritic spines in locus coeruleus NE neurons, enhancing their tolerance to stress stimuli [40]; (2) upregulating the expression of α2-adrenergic receptors in the hippocampus, inhibiting excessive NE release via feedback inhibition [41]; and (3) reducing oxidative damage by scavenging reactive oxygen species through antioxidant enzymes (e.g., superoxide dismutase) produced by *Bifidobacterium lactis* BB-12, reducing oxidative damage to NE neurons [42]. Preclinical studies in innately anxious BALB/c mice demonstrated that *Bifidobacterium longum* 1714 supplementation (1×10^9 CFU/day for 6 weeks) reduced stress-, anxiety-, and depression-related behaviours in the open-field, marble-burying, and forced swim tests, supporting its stress-modulatory and potential sleep-beneficial properties [43]. Translational limitations include species differences in NE neuron plasticity and the lack of validated CSF NE measurement in clinical BD research.

Clinical Relevance: Neuroendocrine Axis Dysfunction in BD

Clinical Relevance: HPA Axis Restoration for Sleep & Cortisol Balance

Impaired negative feedback of HPA axis is a core neuroendocrine abnormality in BD, leading to excessive cortisol secretion and sleep disruption. Specific Bifidobacterium strains (e.g., *B. longum* BB536, *B. lactis* BB-12) may restore HPA axis function through dual pathways, with evidence limited to preclinical *in vivo* models (rodent); human data are restricted to non-BD stress-related disorders. On the one hand, propionate produced by *B. longum* BB536 may hypothetically enhance the binding affinity of glucocorticoid receptors (GR) in the hypothalamus and pituitary gland to cortisol in preclinical models, potentially restoring the normal response of the dexamethasone suppression test in rodents. However, this proposed sequence remains entirely speculative in humans and lacks clinical validation. It is not established that *B. longum* BB536 can stably colonise the human gut to produce sustained propionate levels that enter the systemic circulation, nor is it confirmed that propionate can cross the BBB in patients with BD—even under reduced neuroinflammation—to act on hypothalamic–pituitary GR and modulate pathological hypercortisolemia [44]. In depressive model rats (chronic unpredictable mild stress model), *B. longum* BB536 intervention (1×10^9 CFU/day for 4 weeks; plasma corticosterone measured by radioimmunoassay) reduced peak corticosterone levels by 38% and corrected the flattened diurnal cortisol rhythm [45]. On the other hand, *Bifidobacterium infantis* 35624 may inhibit the NF-κB signalling pathway in immune cells, reducing GR phosphorylation and potentially preventing functional inactivation of GR caused by inflammation [46]. This dual regulation by specific Bifidobacterium strains may break the inflammation-HPA axis hyperactivation cycle, which is particularly relevant for patients with BD and comorbid low-grade chronic inflammation. Key translational constraints include uncertain BBB permeability of propionate in humans with BD, variable gut colonisation efficiency of Bifidobacterium strains in clinical populations, and differences in HPA axis regulation between rodents and humans.

Clinical Relevance: HPT Axis Optimisation for Treatment-Resistant BD

Abnormal HPT axis function (e.g., subclinical hypothyroidism) is common in BD and associated with treatment resistance. Specific Bifidobacterium strains (*B. lactis* BB-12, *B. infantis* 35624) may modulate the HPT axis at three levels, with preliminary clinical evidence in non-BD hypothyroid populations and preclinical data in rodent models; BD-specific data are limited to a small pilot study: (1) enhancing intestinal iodine absorption by regulating the expression of sodium-iodide symporters in intestinal epithelial cells, ensuring sufficient iodine supply for thyroid hormone synthesis [47]; (2) inhibiting the production of thyroid autoantibodies (e.g., anti-thyroperoxidase antibodies) by promoting regulatory T cell (Treg) proliferation, potentially reducing autoimmune interference with thyroid function [48]; and (3) upregulating the expression of thyroid hormone receptors (TRα/β) in the hippocampus, and enhancing the neurotrophic effects of thyroid hormones on neural plasticity [49]. A randomised controlled trial involving 136 hypothyroid patients showed that 8-week supplementation with mainly Lactobacillus and Bifidobacterium strains led to a non-significant clinical and statistical reduction in thyroid-stimulating hormone levels, with no evident alterations in free thyroid hormone levels, thyroid autoantibodies, BMI and medication dosage, while prominently alleviating patients' constipation symptoms [50].

Supplementary Fig. 1 summarises the specific regulatory pathways of Bifidobacterium in the neuroendocrine and sleep dysfunction of BD, involving the interaction be-

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tween the gut and the brain.

Clinically Oriented Future Research Priorities

Future research into specific Bifidobacterium strains as an adjuvant for BD should prioritise precision medicine, tailor interventions to distinct BD subtypes like inflammatory and thyroid variants, and use gut microbiota profiling to identify patients most likely to respond to supplementation. Advancing novel formulations is also important, addressing the variable gut colonisation of current oral forms by developing targeted delivery systems, combining specific Bifidobacterium strains with prebiotics to boost their growth and metabolite production, and exploring synbiotic blends with other beneficial bacteria for synergistic GBA regulation. Critical knowledge gaps demand in-depth mechanistic exploration to clarify how specific Bifidobacterium strains may modulate circadian rhythms via the GBA, alongside large-scale long-term placebo-controlled, randomised clinical trials to validate its potential efficacy for BD-related sleep disturbances and neuroendocrine dysfunction. Multi-omics studies will further uncover specific biomarkers to assess the therapeutic effects of Bifidobacterium for patients with BD. Future research should also directly compare the efficacy of different Bifidobacterium strains in BD and investigate negative or null outcomes to address publication bias.

Conclusions

Specific strains of Bifidobacterium exhibit potential unique advantages in improving sleep quality and regulating neuroendocrine hormone levels in patients with mental disorders through its multi-dimensional regulatory network of "GBA–neurotransmitters–neuroendocrine–immune system." Importantly, its potential adjuvant role in addressing BD-related sleep disturbances and neuroendocrine dysfunction aligns with both the holistic concept of integrative medicine and modern understanding of multi-system pathogenesis of BD. Although preliminary evidence is promising, large-scale, well-designed, placebo-controlled clinical trials are urgently needed to confirm its potential efficacy and safety in BD populations. Notably, some probiotic intervention studies in mood disorders have reported null or minimal effects on sleep and neuroendocrine markers, which underscores the importance of strain selection, patient stratification, and adequate dosing in future BD research. With advances in precision medicine and gut microbiota research, specific Bifidobacterium strains are expected to hold promise as an important component of the comprehensive management system for BD, helping to provide new strategies for improving patients' quality of life, reduce treatment side effects, and enhance long-term prognosis.

Availability of Data and Materials

The datasets used and analysed during the current study were available from the corresponding author on reasonable request.

Author Contributions

CML and XL designed the study; all authors conducted the study; CML and XL collected and analyzed the data. CML and XL participated in drafting the manuscript, and all authors contributed to critical revision of the manuscript for important intellectual content. All authors gave final approval of the version to be published. All authors participated fully in the work, took public responsibility for appropriate portions of the content, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or completeness of any part of the work were appropriately investigated and resolved.

Ethics Approval and Consent to Participate

No.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62641/aep.2237.

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