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Where Mood Meets Microbes: In silico Analysis of Dysbiosis and Its Metabolic Involvements in Major Depressive Disorder

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Abstract: Major depressive disorder (MDD) is a mood disorder that shows up not just in behavior, but physically too. Recent research suggests that microbial dysbiosis may influence MDD by disrupting neurobiological processes, particularly those involving the gut-brain axis (GBA). This study investigated the gut microbiota composition of individuals diagnosed with MDD, specifically examining interactions in the serotonin and butyrate enzymatic pathways. To determine the most significantly altered bacterial groups in MDD patients, qualitative outcome data were gathered from the Disbiome database, while metabolic information was extracted from the KEGG Pathway database. Selected taxa were classified into reduced groups (RedG: *Oscillibacter*, *Faecalibacterium*, *Ruminococcus*) and elevated groups (ElG: *Blautia*, *Anaerostipes*, *Roseburia*). Functional interpretation of these organisms revealed microbial patterns associated with reduced serotonin bioavailability and altered SCFA processing. Tryptophan metabolism appeared skewed toward the kynurenine pathway, while the degradation of neuroactive intermediates such as succinate semialdehyde may be impaired or adaptively buffered. These results support the potential role of gut dysbiosis in MDD symptomatology and reinforce the potential of gut-targeted therapies for mental health conditions.

Key Words: gut microbiome composition; KEGG pathway analysis; Major Depressive Disorder; microbial dysbiosis

1. INTRODUCTION

The 2020 World Health Organization survey found that a total of 1,145,871 Filipinos are affected by clinical depression, otherwise known as Major Depressive Disorder (MDD). MDD is a complex mental disorder typically characterized with symptoms such as anhedonia, a persistent decrease in energy and mood, a loss of interest and pleasure, suicidal thoughts and ideation, and feelings of worthlessness; however, the disorder can also present in different ways, as patients can mask the typical emotion-related symptoms, instead experiencing somatic symptoms such as chronic pain or physical fatigue (Shetty et al., 2018). It is therefore a complicated but common mental disorder. Projections estimated by the WHO predict that MDD will be the leading cause of global disease burden.

Having stated the nature of MDD, being a neurological disorder impacting both mental and physical aspects, it is difficult to pinpoint its cause to a singular root. Instead, MDD exhibits a network of psychosocial, genetic, and biological factors that conglomerate into the disorder's symptoms (Bains and Abdijadid, 2023). Treatment options are available in forms such as therapy and antidepressant medications; however, managing its symptoms can be challenging due to its unpredictability and varying manifestations in patients.

In response to these complexities, digital health technologies have emerged as a promising

advancement in MDD treatment. These tools, capable of gathering and analyzing real-time multimodal data, help address prominent challenges in mental healthcare, such as underdiagnosis, restricted access to providers, and treatment adherence issues (McIntyre et al., 2023). Furthermore, digital health technologies extending into bioinformatics, computational modeling, and data-driven platforms have begun to pave novel solutions and ideas. Specifically, as research increasingly emphasizes the significance of the gut-brain axis in the regulation of mood, the analysis of microbial data and metabolic pathways has become indispensable. These types of interpretations aid in determining how gut microbiota may modulate neurochemical mechanisms associated with conditions such as depression. They enable researchers to identify biological patterns and correlations that would otherwise be undetected in conventional psychiatric evaluations. Integrating these insights into a broader digital health ecosystem could pave the way for more precise, accessible interventions for individuals with MDD.

As previously mentioned, growing attention has been given to the gut-brain axis (GBA) as a potential contributor to neuropsychiatric disorders. The human body was previously estimated to have fewer somatic cells than microbial cells. Recent findings contradict this, showing that the ratio between somatic cells and microbial cells is closer to 1:1, with most of the microbial cells coming from the gastrointestinal tract (GI) (Janssens et al., 2018). Additionally, recent studies have found a bidirectional network between the enteric and central nervous systems known as the gut-brain axis. Dysbiosis, or the disruption of the gut flora, has been implicated in cases of MDD (Dabbousi et al., 2024), as neural pathways and central nervous system (CNS) signals have been implicated to be influenced by microbiota in the GI (Liu et al., 2020).

In particular, the microbiota-gut-brain axis network is moderated via microbial metabolites. Emerging research implicates that the relevant metabolic processes that may contribute to gut dysbiosis in relation to MDD are the synthesis of short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate (Muller et al., 2020), and tryptophan (Lukic et al., 2022). Butyrate is the most physiologically significant of the three primary SCFAs; hence, the bacteria that make it are some of the most beneficial (Fusco et al., 2023). These microbial metabolites directly operate as neurotransmitters, hormones, or immune modulators in place of host metabolites. Alternatively, they may affect host metabolites by working as substrates or signaling molecules to complement multiple processes that cannot be carried out individually (Liu et al., 2020). With that, the microbiota hypothesis has been gaining interest in discussing the origin of mood disorders via GBA.

Considering this context, the current study examines the gut microbiota in patients diagnosed with MDD. The specific objectives are to determine the most significantly altered groups of bacteria in patients diagnosed with MDD, with bacteria being classified into either elevated (ElG) or reduced groups (RedG), and to analyze the associated metabolic pathways of the selected ElG and RedG microbes.

To situate these objectives within the broader body of work, numerous studies have found a positive correlation between gut microbiota and MDD (Simpson et al., 2023). An increasing amount of research suggests that the gut microbiota influences mental health via the gut-brain axis. For instance, a study by Palsson and Drossman found that there is strong evidence of gut dysbiosis in patients with inflammatory bowel syndrome, and up to 30% of individuals are diagnosed with MDD. However, Dabbousi noted that there is still insufficient evidence regarding changes in gut bacterial composition associated with MDD. Thus, this study has the potential to advance knowledge further and give insight into the relationship between gut microbial dysbiosis and MDD. It may also help identify novel therapeutic targets, such as microbiome-based medications, from an understanding of these microbial alterations and provide more individualized and efficient medication for each case. The use of computational tools such as the Disbiome database and KEGG allows for a thorough analysis of the microbiome and may potentially reveal metabolic pathways that are involved in MDD, thereby serving as a framework for further studies and research.

2. METHODOLOGY

Sample data as of September 2024 was extracted from Disbiome. “Major depressive disorder” was inputted as the search query item, of which fecal samples in human patients were deemed findings. Records were exported using the Disbiome JSON web service, converted to CSV, then XML, and separated into “elevated” (ElG) and “reduced” (RedG) groups based on qualitative outcomes.

The microbial taxa selected for metabolic pathway analysis were chosen based on their frequency of occurrence in the dataset, with priority given to those with the highest representation in both the ElG and RedG groups. The selected organisms include *Oscillibacter*, *Faecalibacterium*, and *Ruminococcus* for the RedG and *Blautia*, *Anaerostipes*, and *Roseburia* for the ElG.

The metabolic pathway analysis investigated two MDD-related pathways, specifically, butyrate and tryptophan metabolism. These pathways were explored using KEGG pathway entries already available for the selected organisms. Butyrate metabolism (map00650) was chosen due to its role in producing short-chain fatty acids (SCFAs) that regulate inflammation and influence the gut-brain axis. On the other hand, tryptophan metabolism (map00380) was explored due to its involvement in serotonin and melatonin production, both relevant to mood regulation and sleep patterns. The representative organisms selected for each taxon, such as *Roseburia intestinalis* and *Blautia wexlerae,* were chosen because they have been located in the human gut.

3. RESULTS AND DISCUSSION

3.1 KEGG Pathway Analysis for Tryptophan Metabolism

3.1.1 ElG Microbes

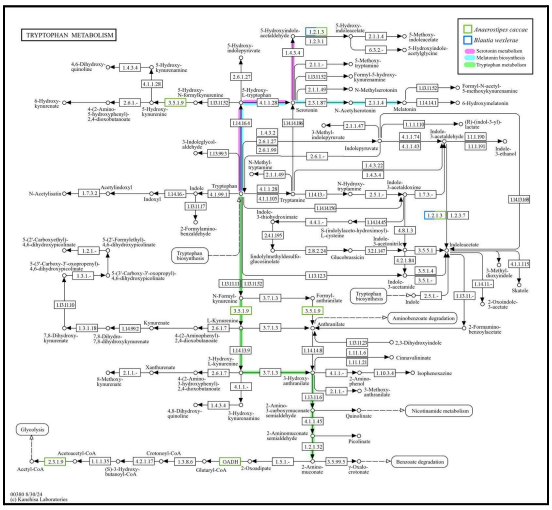

Fig. 1. Annotated tryptophan metabolism of ElG microbes.

Tryptophan is an essential amino acid metabolized via two major pathways: the kynurenine pathway (green) and melatonin biosynthesis (pink). Figure 1 provides the following information. In the kynurenine pathway, tryptophan is converted to N-formyl-kynurenine by indoleamine 2,3-dioxygenase (EC 1.13.11.52) or tryptophan 2,3-dioxygenase (EC 1.13.11.11), then to L-kynurenine by arylformamidase (EC 3.5.1.9), an enzyme found in *A. caccae*. However, further conversion of L-kynurenine into metabolites like 3-hydroxy-L-kynurenine or 3-HAA does not occur in ElG microbes due to the absence of necessary enzymes.

In the melatonin pathway, tryptophan is converted into serotonin and melatonin via enzymes such as tryptophan hydroxylase (EC 1.14.16.4), DOPA decarboxylase (EC 4.1.1.28), aralkylamine N-acetyltransferase (EC 2.3.1.87), and acetylserotonin O-methyltransferase (EC 2.1.1.4)—all of which are also absent in ElG microbes. Serotonin, when degraded by serotonin deaminase (EC 1.4.99.3), is converted to 5-hydroxyindoleacetaldehyde and further oxidized to 5-hydroxyindoleacetate by aldehyde dehydrogenase (EC 1.2.1.3), which *A. caccae* and *B. wexlerae* possess.

Roseburia sp. is excluded from the figure due to lacking any annotated tryptophan metabolism pathways in KEGG.

3.1.2 RedG Microbes

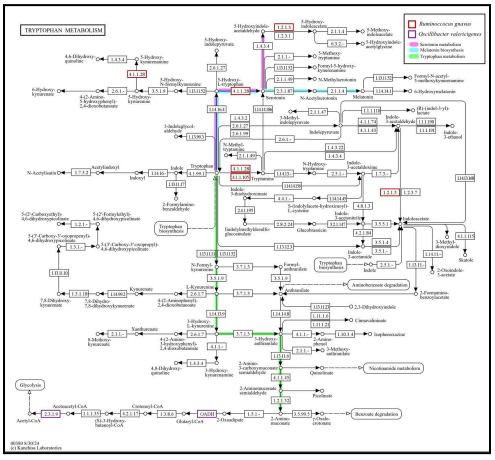

Fig. 2. Annotated tryptophan metabolism of RedG microbes.

As illustrated in Figure 2, neither *R. gnavus* nor *O. valericigenes* possesses the full suite of enzymes for tryptophan metabolism. However, *R. gnavus* is involved

in the tryptamine pathway through the presence of both aromatic-L-amino-acid decarboxylase (EC 4.1.1.28) and L-tryptophan decarboxylase (EC 4.1.1.105), enabling the conversion of tryptophan into tryptamine. Although aldehyde dehydrogenase (EC 1.2.1.3) is also present in *R. gnavus*, it is not used in this pathway due to the absence of aldehyde intermediates. Unlike ElG microbes, *R. gnavus* overlaps with serotonin biosynthesis via aromatic-L-amino-acid decarboxylase (EC 4.1.1.28), supporting the conversion of 5-hydroxy-L-tryptophan into serotonin. While it lacks enzymes for further serotonin degradation, the presence of this activity may indicate a host-favored bias toward the serotonin–melatonin pathway rather than the kynurenine route. Both *R. gnavus* and *O. valericigenes* express aldehyde dehydrogenase (EC 1.2.1.3), similar to ElG microbes, but do not possess aldehyde oxidase (EC 1.2.3.1).

Like *Roseburia* sp., *Faecalibacterium* sp. is excluded from the diagram due to lacking annotated tryptophan metabolism in the KEGG database.

3.1.3 Pathway Comparisons and Mood Implications

ElG microbes catalyze numerous tryptophan metabolic reactions, producing neurotransmitter precursors such as kynurenine, serotonin, and melatonin accessible in the human host through the GBA.

The kynurenine pathway, in which the ElG microbe *A. caccae* is involved through the expression of arylformamidase (EC 3.5.1.9), demonstrates lowered serotonin and melatonin levels due to a natural preference for tryptophan redirection to kynurenine. If tryptophan synthesized by *A. caccae* is primarily diverted to this pathway, less remains available for the biosynthesis of serotonin and melatonin. Thus, increased levels of *Anaerostipes* sp. may exacerbate mood-related symptoms due to the lack of necessary enzymes for producing serotonin and melatonin instead.

This could be further compounded by reduced populations of *Ruminococcus* sp. due to their enzymatic capability of serotonin synthesis. Studies elucidate that high kynurenine levels can increase the risk of developing depression (Zong et al., 2024) and cognitive impairments (Gao et al., 2019); however, the anti-inflammatory properties arising from outputs of the kynurenine pathway could have neuroprotective effects.

Serotonin and melatonin are important neurotransmitters that indirectly regulate mood (Bamalan et al., 2023). When biosynthesized by microbes, they cannot be absorbed by the human host's brain due to the blood-brain barrier. Instead, they involve themselves through gut cellular signaling (Liu et al., 2021). Take 5-hydroxytryptamine receptor 4, for example, a type of serotonin receptor found in enteric neurons that participates in neurogenesis through cyclic adenosine monophosphate production and protein kinase A activation. Additionally, low serotonin levels in the gut contribute to a reduction of enteric neurons, consequently reducing gastrointestinal mobility (Israelyan et al., 2019). Related literature suggests that constipation can present as a comorbid condition to depression and vice versa. Individuals with chronic constipation were found to have a 48% higher risk of developing depression than those without (Yun et al., 2024), and 24.6% of those depressed individuals reported having problematic bowel movements (Ballou et al., 2019). These examples serve as pieces of the puzzle in serotonin's capacity to regulate numerous bodily functions like peristalsis, vasoconstriction, and GI secretion.

Meanwhile, when it comes to the involvement of *R. gnavus* in tryptamine production through both aromatic-L-amino-acid decarboxylase and L-tryptophan decarboxylase (EC 4.1.1.28 and 4.1.1.105, respectively), lowered levels of *Ruminococcus* sp. may indicate decreased tryptamine bioavailability. Tryptamine serves as one of the intermediates to serotonin (Kang et al., 2007) through hydroxylation. It plays an influential role in gut motility and the GBA due to its gut-signaling behavior.

Indeed, alterations in gut serotonin levels accompanied by the elevation of *Anaerostipes* sp. and reduction of *Ruminococcus* sp. reveal a dual interaction that may not necessarily be described through a direct cause-and-effect relationship. Particularly noteworthy is the outcome of reduced serotonin production, whether it be through pathway diversion or downregulation of catalyzed conversions, leading to lower gut concentration levels, in turn cascading to gut serotonin's maintenance roles.

3.2 KEGG Pathway Analysis for Butyrate Metabolism

3.2.1 ElG Microbes

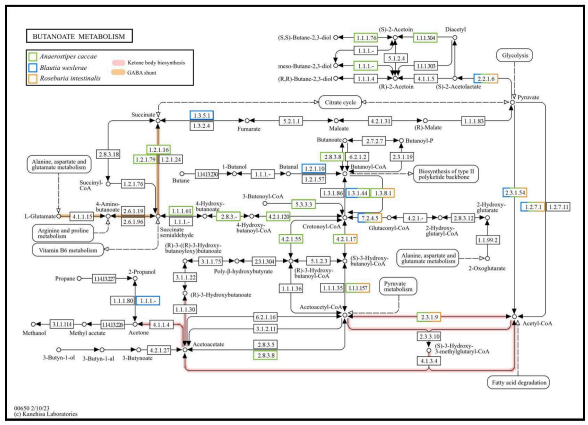

Fig. 3. Annotated butyrate metabolism of ElG microbes.

Figure 3 depicts the capacity of the 3 different ElG microbes in processing key intermediates such as acetyl-CoA, crotonoyl-CoA, and butanoyl-CoA. All three possess formate C-acetyltransferase (EC 2.3.1.54) and pyruvate synthase (EC 1.2.7.1), enabling acetyl-CoA production from various substrates. *A. caccae* and *B. wexlerae* share enzymes including acetyl-CoA C-acetyltransferase (EC 2.3.1.9), 3-hydroxybutyryl-CoA dehydrogenase (EC 1.1.1.157), and acetolactate synthase (EC 2.2.1.6), facilitating the conversion of acetyl-CoA to crotonoyl-CoA. However, only *A. caccae* can continue to carry crotonoyl-CoA through to butanoyl-CoA and finally to butyrate via butyryl-CoA:acetate CoA transferase (EC 2.8.3.8). In addition, *A. caccae* uses vinylacetyl-CoA delta-isomerase (EC 5.3.3.3) and 3-hydroxybutyryl-CoA dehydratase (EC 4.2.1.55) to act on alternate substrates.

A. caccae is also capable of converting crotonoyl-CoA to succinate through intermediates such as 4-hydroxy-butyrate (GHB) and succinate semialdehyde, using succinate-semialdehyde dehydrogenases (EC 1.2.1.16 and EC 1.2.1.79). Meanwhile, *R. intestinalis* contributes reversibly via butyryl-CoA dehydrogenase (EC 1.3.8.1), and *B. wexlerae* uniquely expresses acetylating acetaldehyde dehydrogenase (EC 1.2.1.10) to produce butanoyl-CoA from butanal. Both *A. caccae* and *B. wexlerae* possess succinate dehydrogenase (EC 1.3.5.1), linking butyrate metabolism to the TCA cycle. Altogether, *A. caccae* stands out for its broader metabolic reach and potential buffering role in SCFA-associated dysbiosis.

3.2.2 RedG Microbes

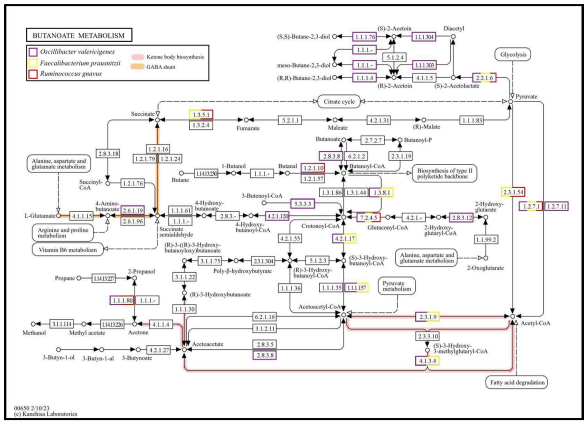

Fig. 4. Annotated butyrate metabolism of RedG microbes.

Figure 4 informs of the following. Similar to ElG microbes, RedG microbes like *O. valericigenes*, *R. gnavus*, and *F. prausnitzii* utilize acetyl-CoA as a central precursor across multiple KEGG metabolic branches. All three express pyruvate synthase (EC 1.2.7.11) and acetolactate synthase (EC 2.2.1.6), supporting pathways such as pyruvate formation and 2,3-butanediol fermentation. Notably, *O. valericigenes* expresses nearly all the enzymes required to yield diacetyl and meso-butane-2,3-diol, with broader coverage than *A. caccae*. Both ElG and RedG microbes also demonstrate overlap in ketogenesis via enzymes like acetyl-CoA C-acetyltransferase (EC 2.3.1.9) and butyryl-CoA:acetate CoA transferase (EC 2.8.3.8), though RedG microbes like *F. prausnitzii* additionally express hydroxymethylglutaryl-CoA lyase (EC 4.1.3.4), enabling formation of (S)-3-hydroxy-3-methylglutaryl-CoA.

While CoA-linked intermediates are active across both groups, some enzymes are absent in RedG microbes, such as 3-hydroxybutyryl-CoA dehydratase (EC 4.2.1.55), trans-2-enoyl-CoA reductase (EC 1.3.1.44), and CoA transferase (EC 2.8.3.12), which may limit carbon flow flexibility and impact gut-brain signaling. Finally, *O. valericigenes* possesses GABA transaminase (EC 2.6.1.19), linking it to the GABA shunt by converting GABA into succinate semialdehyde.

3.2.3 Pathway Comparisons and Mood Implications

With respect to the succinate metabolic pathway involving the three specific substrates (GABA, succinate semialdehyde, and succinate), a potential tandem between the elevated and reduced microbes could be observed.

O. valericigenes can catalyze the conversion of GABA to succinate semialdehyde using GABA transaminase. Succinate semialdehyde has been described as a relatively unstable intermediate (Pearl et al. 2009); it is further degraded to succinate through succinate-semialdehyde dehydrogenase with either NAD^+ or $NADP^+$ as an acceptor. As seen in Figure 3, *A. caccae* can carry out this reaction (EC 1.2.1.16 and 1.2.1.79) using $NADP^+$ specifically.

A complementary mechanism reveals itself, wherein the RedG microbe, *O. valericigenes,* is capable of converting GABA to succinate semialdehyde but lacks the enzymes to further process its degradation. Meanwhile, the ElG microbe *O. valericigenes* is not involved in the reversible reaction between GABA and succinate semialdehyde but can further process environmental succinate semialdehyde into metabolites such as succinate or GHB.

Succinic semialdehyde dehydrogenase deficiency, or gamma-hydroxybutyric aciduria (SSADH), marked by an accumulation of succinate semialdehyde and, subsequently, the alternative by-product GHB, has been associated with neurological and psychiatric dysfunction (Knerr et al., 2007; Knerr et al., 2008). A case report by Gibson et al. (2003) observed SSADH patients displaying behavioral disturbances and psychosis characterized by disturbed sleep, anxiety, aggression, and hallucinations. Similarly, Kneer et al. (2008) examined thirty-three patients and found that twenty-seven (82%) of the participants presented attention deficit, aggression, hyperactivity, anxiety, and obsessive symptoms, among others. Fifteen patients (45%) also manifested issues with sleep, such as difficulties in sleep maintenance.

With this, KEGG metabolic findings suggest potential adaptive dysbiosis in the gut microbiota of depressed patients. Belkaid and Hand (2014) describe an interplay between gut bacteria and host immunity in maintaining homeostasis, stating the likelihood of a reciprocal “immune system-gut microbiota cooperation." Thus, in patients exhibiting depressive or mood-related symptoms, the host immune system may alter microbial populations in an attempt to alleviate these traits. Because the accumulation of succinic semialdehyde may be implicated in neuropsychiatric behaviors, this dysbiotic state may serve as a buffer against stressors like succinic semialdehyde. Because *O. valericigenes* possesses GABA transaminase but no other enzymes for further degradation, the body may attempt to suppress *Oscillibacter* sp. populations to halt symptom exacerbation. On the other hand, *A. caccae* is characterized by its functional proficiency in converting succinate semialdehyde to various intermediates, such as GHB all the way to crotonoyl-CoA, or to succinate, where it may proceed to the TCA. These beneficial routes may lead to increased modulation of *Anaerostipes* sp. populations for upregulation. Gut dysbiosis may not necessarily arise from a pathological state but may potentially result as a means to buffer or manage symptoms caused by stressors such as elevated succinic semialdehyde levels.

4. CONCLUSIONS

Of the 45 microbes and their qualitative outcomes extracted from Disbiome, *Oscillospiraceae* (*Oscillibacter*, *Faecalibacterium*, *Ruminococcus*) were filtered and assigned to RedG, while *Lachnospiraceae* (*Blautia*, *Anaerostipes*, *Roseburia*) were for ElG. Functional analyses of KEGG pathways—tryptophan (map00380) and butyrate metabolism (map00650)—were performed, and key findings are as synthesized below.

Both the elevation of *Anaerostipes* sp. and the reduction of *Ruminococcus* sp. were associated with decreased gut serotonin levels, either through reduced 5-HTP to serotonin conversion or redirection to the kynurenine pathway. This demonstrates that different microbial shifts can converge to disrupt serotonin bioavailability.

This paper also proposes that host immune response may influence gut populations in modulating concentrations of succinate semialdehyde levels as an adaptive dysbiotic measure. *Oscillibacter* sp., which can produce but not degrade succinate semialdehyde, may be downregulated, while *Anaerostipes* sp., capable of processing intermediates without forming succinate semialdehyde, may be favored.

The results, all in all, emphasize the role of gut microbiota in modulating host neurochemistry. Future

studies using fecal samples and transcriptome analysis in MDD patients may validate these interactions and expand into related mental illnesses with overlapping pathophysiology.

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