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The Impact of the Circadian Rhythms on Micronutrient Absorption

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Abstract

The term malnutrition consists of both under and over-nutrition. However, micronutrient deficiencies are common in both situations. Micronutrient deficiencies or 'Hidden hunger' are the underlying cause of the chronic intergenerational cycle of malnutrition. Various strategies and policies have been rolled out throughout the globe to mitigate the challenges. However, population studies have revealed that the impact of existing policies is not enough to eradicate the problem. The amalgamation of chronobiological approaches in planning nutrition intervention strategies may be beneficial to address the insurmountable problem. This review emphasizes the association of recent advancements in chronobiology in the mitigation of micronutrient-related challenges. Attempts have also been taken to understand the possible links among gut microbiota, micronutrient absorption, and circadian rhythm based on available research results. If this complex relation is properly understood then it may help in planning population-based intervention strategies for lower-middle-income group of countries, like India.

Keywords: Circadian rhythm, Micronutrient, Gut microbiota, Malnutrition, Chrononutrition

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Introduction

Malnutrition is a global concern. India is one of the major contributors of malnourished individuals in the world. Various public health strategies and policies have been implemented to eradicate the problem (Rajpal et al., 2020). The rate of success in alleviating malnutrition is slow. However, several approaches have been implemented but outcomes are not satisfactory. With the remarkable improvement in the production and distribution of food, the country secures the macronutrient demand of individuals but the micronutrient requirements remain neglected (Stevens et al., 2022). Thus, the exploration of newer approaches to counter the severity of malnutrition is needed. Hence the crosstalk between chrononutrition and micronutrient absorption kinetics is a fascinating area of research. The intricate relationship between the timing of nutrient consumption and the body's ability to absorb the essential micronutrients needs to be explored (Mao et al., 2023). Understanding how the body's internal clock, or circadian rhythm, influences the absorption of micronutrients has significant implications for public health and clinical nutrition.

This exploration aims to uncover the interplay between chrononutrition and micronutrient absorption kinetics, shedding light on how our dietary patterns and timing of food intake can impact overall nutrient utilization and health outcomes. Recent studies have demonstrated that the timing of nutrient intake can influence the body's ability to absorb and utilize essential micronutrients such as vitamins and minerals. For example, the absorption of certain minerals like iron and zinc is influenced by the body's internal clock (Celep and Rastmanesh, 2016). This suggests that the timing of nutrient consumption may play a crucial role in maximizing the bioavailability of these micronutrients.

Additionally, the concept of chrononutrition emphasizes aligning food intake with the body's natural rhythms to optimize metabolism and nutritional status. By understanding how the body's circadian rhythm influences the absorption kinetics of micronutrients, we can tailor dietary recommendations and meal timings to improve nutrient uptake and overall health (Oike et al., 2014). In this review, we will delve into the mechanisms underlying the crosstalk between chrononutrition and micronutrient absorption kinetics, highlighting the potential implications for personalized nutrition strategies and the development of chrono-specific dietary recommendations. By unravelling the intricate relationship between the timing of nutrient consumption and micronutrient absorption, we can uncover valuable insights that may ultimately

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contribute to improved health outcomes and disease prevention.

Micronutrient deficiencies in developing countries

Micronutrient deficiencies in several developing countries including India are a significant public health concern, affecting a large portion of the population (Stevens et al., 2022). According to the NFHS, several micronutrient deficiencies are prevalent in India, with a particular focus on deficiencies of vitamin A, iron, iodine, and zinc (Awasthi et al., 2022). Vitamin A deficiency is a pressing issue, especially among children and pregnant women. It can lead to vision impairment and weakened immunity, making individuals more susceptible to infections (Feskens et al., 2022). Iron deficiency is also widespread, leading to anemia, fatigue, and impaired cognitive development, particularly in children (Pollitt et al., 1986). Iodine deficiency, primarily in the form of goiter, affects thyroid function and can lead to developmental issues (Rohner et al., 2014). Zinc deficiency is another concern, impacting growth, immune function, and overall health (Venkatesh et al., 2021).

These deficiencies are often exacerbated by inadequate dietary diversity, socio-economic disparities, and limited access to fortified foods and supplements. Addressing these micronutrient deficiencies requires a multi-faceted approach that includes promoting diverse and balanced diets, fortifying staple foods, and providing targeted supplementation, especially for vulnerable populations like young children and pregnant women (Nair et al., 2016). Efforts to address micronutrient deficiencies in India can benefit from considering the interplay between chrononutrition and micronutrient absorption kinetics. By aligning nutritional interventions with the body's natural rhythms, we can optimize the absorption and utilization of essential micronutrients, thus contributing to improved health outcomes at the population level (Palomar-Cros et al., 2023). This may involve strategically timing nutrient-rich meals and addressing cultural and behavioral factors that influence food consumption patterns. Integrating chrono-specific dietary recommendations into existing public health initiatives could potentially enhance the effectiveness of interventions aimed at combating micronutrient deficiencies in India (Madhari et al., 2020).

In developing countries including India, the major bottlenecks are the higher prevalence of stunting and anemia among the population especially among the under-five children which restricts the growth of the nation (Stevens et al., 2022). As the children are the future foundation of the nation if they have been diagnosed with chronic forms of undernutrition, the chances of achieving the higher demographic dividend is reduced. Thus, for planning of intervention strategies various approaches

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including chronobiology are crucial to mitigate the insurmountable problems. . The consequences of micronutrient deficiency in children of India have been shown as an example in
Figure 1.

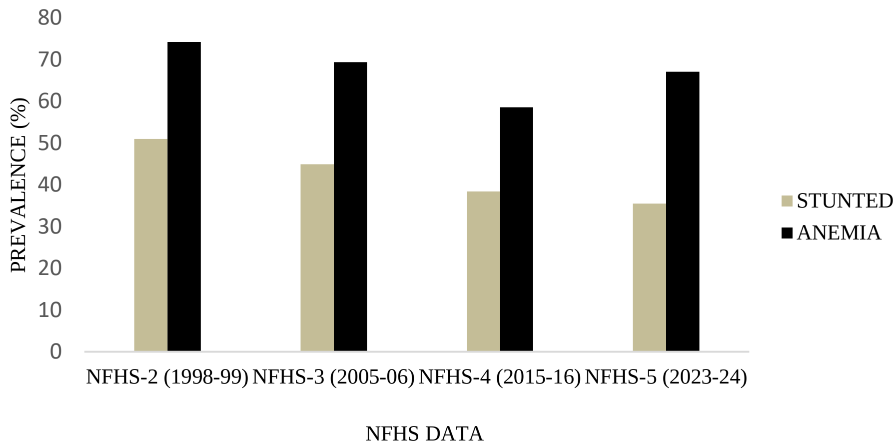

Figure 1. The reflection of the consequences of major micronutrient deficiencies for the last twenty-five years

Chrononutrition

Chrononutrition, also known as time-based nutrition, examines the impact of meal timing on our body's metabolic processes, including the absorption and utilization of nutrients. This concept revolves around the idea that our biological clock, or circadian rhythm, influences our body's response to food intake throughout the day (Franzago et al., 2023). Various research has shown that different nutrients are absorbed and processed differently at various times of the day. For example, the body's ability to utilize carbohydrates and fats may vary based on the time they are consumed, while protein absorption kinetics can also be influenced by meal timing (Challet, 2019). Additionally, micronutrients such as vitamins and minerals, which were previously mentioned, are known to exhibit varying absorption rates at different times (Beaulieu et al., 2020). In practical terms, chrononutrition involves strategically timing meals and nutrient intake to optimize the body's processing and utilization of nutrients. For instance, breakfast, known as the "break-fast," plays a critical role in jump-starting our metabolism after the overnight fasting period. Ensuring a balanced and nutrient-rich breakfast may have a positive impact on our energy levels and cognitive function

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throughout the day (Gutierrez Lopez et al., 2021).

Moreover, aligning the consumption of certain micronutrients with their optimal absorption periods can be beneficial. For instance, consuming vitamin D-rich foods during the morning hours might coincide with the body's enhanced ability to absorb and utilize this essential nutrient (Picciano, 2023). From a personalized nutrition perspective, understanding chrononutrition allows for tailored dietary recommendations that account for an individual's unique circadian rhythm and metabolic profile. By considering an individual's natural eating patterns and the specific times when their body is most receptive to certain nutrients, personalized nutrition plans can be designed to maximize nutrient absorption and overall metabolic efficiency (Corbin et al., 2023).

In the context of addressing micronutrient deficiencies, integrating chrono-specific dietary guidelines into public health initiatives in India could offer a promising approach. By leveraging the insights of chrononutrition to optimize the absorption of vital micronutrients, targeted interventions can be developed to address the prevalent deficiencies and improve the overall nutritional status of the population. In the subsequent sections of this review, we will delve deeper into the specific mechanisms and practical implications of chrono-specific dietary strategies, aiming to provide a comprehensive understanding of how the interplay between chrononutrition and micronutrient absorption can be harnessed for improved health outcomes.

Micronutrient absorption kinetics

Maintaining a healthy gut flora is vital, and one method to do so is to consume an adequate number of prebiotics and probiotics. Consuming fermented foods and other probiotic sources can help maintain a healthy digestive tract, gut microbiota activity, and general nutritional status (Leeuwendaal et al., 2022). Apoptosis can be triggered by a variety of signals that colonocytes receive. For example, large levels of short-chain fatty acid butyrate in the intestinal lumen can cause acidosis and cell death (Schulthess et al., 2019) Thus, it stimulates the ZnR/GPR39-dependent MAP kinase and AKT pathways, resulting in increased amounts of the pro-survival glycoprotein clusterin (Cohen et al., 2014). Experiment results reveal that ZnR/GPR39 (Zinc sensing Receptor/G-protein coupled receptor 39) may have a broader role than colonocytes alone. It is because luminal Zn^{2+} accelerates gastric ulcer recovery, possibly due to accelerated cell proliferation mediated by ZnR/GPR39. In colonocyte cell cultures, ZnR/GPR39 activation increases the expression of zonula occludens-1 and occludin, both of which are tight junction (TJ) proteins (Hershfinkel, 2018). These proteins are essential components of the intestinal barrier that help keep it intact. Thus, higher

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levels of intestinal integrity stimulate intestinal stem cells to replenish Paneth cells, reducing inflammation via boosting zinc uptake (Azriel-Tamir et al., 2004). ZIP4 expression increases at the apical location of the gut, promoting zinc uptake. The basolateral location of enterocytes, which makes up ZnT1, releases zinc into the bloodstream. Thus, plasma-level zinc sufficiency is reached, with a considerable impact on iron absorption (Palsa et al., 2019). Initially, it was thought that iron and zinc could compete for absorption at divalent metal ion transporter-1 (DMT1) in intestinal cells because of their similar atomic radius and oxidation states. DMT1 is an apical iron transporter in intestinal cells that works via proton coupling. In intestinal cell models, acidic pH promotes iron uptake but not zinc uptake (Yu et al., 2019). Furthermore, in Caco-2 cells, the neutralizing antibody to DMT1 did not affect zinc absorption, indicating that DMT1 is not engaged in zinc transport. Even the experiments demonstrated that zinc treatment of intestinal cells increases iron absorption, which is attributed to increased DMT1 mRNA and protein expression (Ma et al., 2006). Zinc increases iron absorption in the gut by stabilizing DMT1 mRNA via IRP2 activation, which leads to enhanced DMT1 protein expression. This route requires the activation of PI3K signaling. Zinc also increases FPN1 expression in Caco-2 cells and accelerates iron escape via the basolateral pathway. MTF1 appears to mediate these effects through metal transcription factor-1 (Liu et al., 2023). Zinc has been shown to increase the expression of the mTORC1 pathway, which is a master regulator of DMT1 promotion (Niles et al., 2023). Thus, we might hypothesize that an appropriate prebiotic and probiotic diet promotes GPR39 expression in colonocytes. These greater levels of expression reinforce the epithelium's integrity via TJ proteins. TJ proteins enhance intestinal regeneration, causing the ZIP4 transporters at the apical location of enterocytes to absorb zinc (Huebner et al., 2023). Interestingly, plasma zinc sufficiency increases enterocytes' iron absorption proficiency.

Chrononutrition & Micronutrient absorption

Circadian rhythms have been observed in various organisms, from primitive cyanobacteria to mammals. Cells possess internal circadian clocks that control multiple physiological processes (Lopez et al., 2021). The molecular mechanism of the circadian clock involves a network of transcriptional pacemakers found in almost all cells within the body. This auto-regulatory system is made up of interconnected transcriptional-translational feedback loops and regulates rhythmic expression of both activating and repressing elements, leading to rhythmic expression of downstream clock-controlled genes (Cox & Takahashi, 2019). Essential components include Clock and Bmal1 as

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activators, while Per1/2, Cry1/2 function as core repressors (Asher, G & Sassone-Corsi, P. 2015). In addition to these core elements, ancillary regulators such as Rev-erbα, Rorα, Nfil3, and Dbp offer redundant functions and secondary regulation for the core clock.

The primary regulator for oscillation, also known as the central pacemaker, is situated in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus in the brain. It is synchronized by light/dark signals transmitted through stimulation of the optic nerve. The SCN clock communicates temporal information via neurotransmitters to non-SCN clocks located in other brain regions and peripheral organs (Patke et al., 2019). The circadian system influences activity at various levels. In multicellular organisms, activities requiring coordination of the whole organism such as arousal, feeding behavior, and locomotor activity exhibit daily rhythmic patterns controlled by the circadian system defining time-dependent energy intake and expenditure patterns (Serin & Tek, 2019). Organ and tissue-level metabolic fluxes are driven by predictive and adaptive mechanisms where transcription factors regulated by circadian rhythms control gene expression patterns of metabolic enzymes (Thurley et al., 2017). Adaptive responses are activated by cellular receptors triggered by signaling molecules with diurnal variations controlled by both central nervous system input from SCN as well as physiological feedback loops involving metabolites and energy-related hormones leading to epigenetic regulation that reinforces synchronization across peripheral circadian clocks (Keßler & Pivovarova-Ramich, 2019). The hierarchical relationship between different aspects of these processes ensures optimal circadian rhythms coordinating light exposure, physical activity routines, nutritional habits, and sleep/wake cycles for achieving homeostasis.

Peripheral oscillators respond to signals not dependent on the suprachiasmatic nucleus, such as changes in neurohumoral activity caused by fasting/feeding cycles and physical movement. These signals include energy-related hormones like ghrelin, leptin, insulin, and glucocorticoids, as well as signaling pathways such as AMP-activated protein kinase [AMPK], peroxisome proliferator-activated receptors [PPARs], and sirtuin-1 [SIRT1] (Cao et al., 2023). Peripheral oscillators control local functions including hormone release, immune response, and digestion, while SCN signals ensure synchronization with peripheral clocks. The presence of a transcriptional circadian clock in nearly every cell suggests that metabolic functions' rhythmicity is crucial for health (Poggiogalle et al., 2018). Disruption to the circadian system occurs when activities like sleep or eating are out of sync with the external environment's dark/light patterns leading to disturbances in homeostasis. Increasing epidemiological evidence indicates that a sedentary lifestyle; a Western diet high in fat and refined carbs but low in fibre; along with behaviours such shift work, and chronic sleep deprivation all contribute to global overweight/obesity epidemics. Even leads to cardiovascular disease and other metabolic disorders (Kervezee et al., 2018).

In reaction to dietary inputs, the bacterial components of the gut microbiota communicate with the host epithelium by releasing metabolites known as microbial-associated molecular patterns (MAMPs) (Aburto & Cryan, 2024). These MAMPs consist of short-chain fatty acids such as acetate, butyrate, and propionate; polyamines like spermine; amino acids including tyrosine and tryptophan along with their fermentation products such as taurine, histamine, and indole; biotin; vitamin K; γ-aminobutyric acid; bile acids transferred from host-secreted bile acids into secondary bile acids; and lipopolysaccharide (Hussain & Pan, 2015). All these MAMPs can act as signaling molecules that potentially influence host metabolism and energy equilibrium.

Rhythmic changes in gene expression controlled by the circadian clock allow for the temporal organization of fundamental physiological processes, including immune function (Man et al., 2016). Elements of the immune response that exhibit circadian patterns of expression, such as pattern recognition receptors like Toll-like receptors and nucleotide-binding oligomerization domain-like receptors, detect microorganisms through MAMPs (Scheiermann et al., 2013). Furthermore, research indicates that genes in microorganisms themselves, such as 10% of genes in *Trypanosoma brucei* which causes sleeping sickness, also demonstrate circadian behavior (Rijo-Ferreira et al., 2017). The internal biological clock prepares for daily fluctuations in infection risk by triggering a stronger immune response at the beginning of the active phase within a light-dark cycle (Abele et al., 2019).

The gastrointestinal tract and the gut microbiota work closely together to process various inputs, such as light and nutrient availability, through molecular patterns associated with microbe-associated molecular patterns signals. The potential signaling pathways responsible for transmitting MAMP signals from the microbiota also play a role in activating immune responses against pathogen invasion (Najafi et al., 2023). These pathways include c-Fos, TLRs, nuclear factor κB, Jun N-terminal protein kinase, CyclinD, and mitogen-activated protein kinase. Beneficial members of the gut microbiota community may impact host balance by leveraging established signaling pathways that affect peripheral clock-controlled genes' rhythmicity and host gene expression (Murakami & Tognini, 2020). The G protein coupled receptors further

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trigger the MAPkinase/AKT pathway to modulate the trans junctional proteins like occludin. The higher expression of occludin may affect the intestinal stem cells which further activates the Paneth cells (Cohen et al., 2014). The evidence showed that during the recovery phase of the enterocytes, the Paneth cells activate the Zinc importer protein Zinc importer 4 (ZIP4). The increased expression ZIP4 at the apical cite of the enterocytes will enhance the availability of zinc at the enterocytic region. Thus, influx of zinc promotes the PI3K/mTOR pathway, which further activates ferroportin (FPN), hephaestin (HEPH) and iron-responsive element binding protein 2 (IRP2). The activated FPN, HEPH and IRP2 improves availability of iron basolateral cite of the enterocytes to induce the DMT1 signalling (Williams & Mills 1970). Even concomitant activation of ZIP4 and DMT1 receptors, enhances plasma zinc and iron levels, which further activates growth signaling pathways essential to be activated for the development of chondrocytes (Palsa et al., 2020). (Figure 2) (Figure 3)

The underdevelopment of chondrocytes is considered as one of the reasons for the stunting. Even increased plasma zinc, enhances the capacity of carbonic anhydrase enzymes, essential for the activation of stomach HCl. The optimum production of HCl helps in the absorption of iron by releasing iron from the complex bolus forms of food (Anderson & Frazer, 2017). Thus, the timely regulated lifestyle modification could help in the improvement of the micronutrient status of the individual. However, the data to confirm the impact of circadian rhythm and micronutrient absorption kinetics are from animal studies, to plan intervention strategies human studies especially randomized control trials are needed to implement the result outcomes at the population level.

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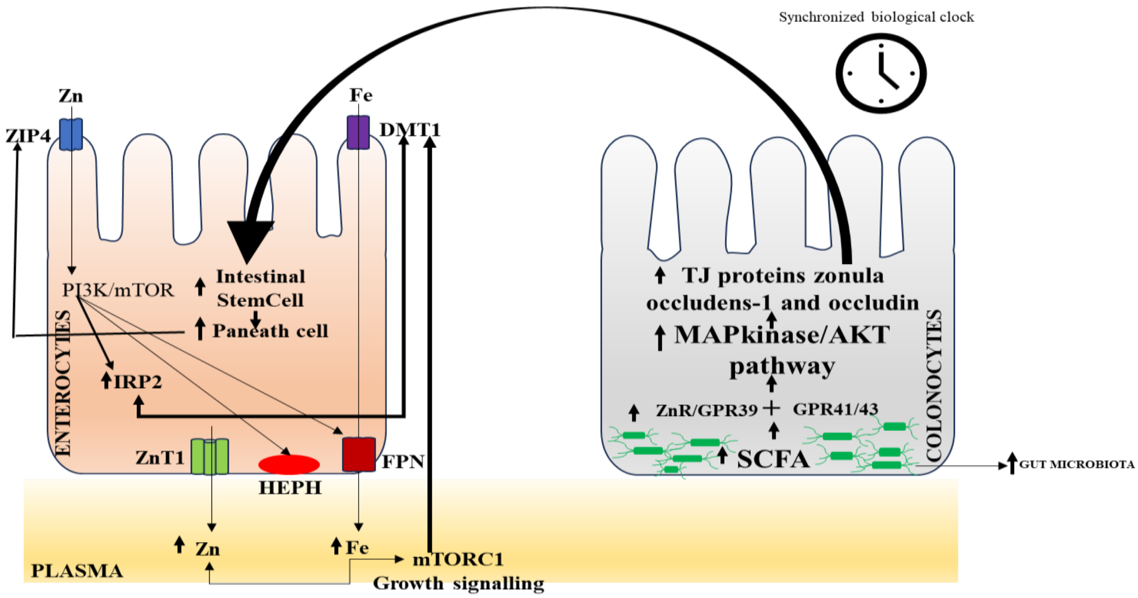

Figure 2. Hypothetical model for effects of synchronization of circadian rhythm on intestinal zinc and iron absorption. During adequate consumption of prebiotics and probiotics, an increased level of zinc available in the intestinal lumen stimulates intestinal iron transport via PI3K-IRP2-DMT1 and FPN1. Adequate zinc can reduce inflammation and prevent it from inhibiting iron absorption. Additionally, sufficient zinc induces the mTORC1 pathway that controls growth signalling, and may increase the body's need for iron, leading to better absorption of iron in the body.

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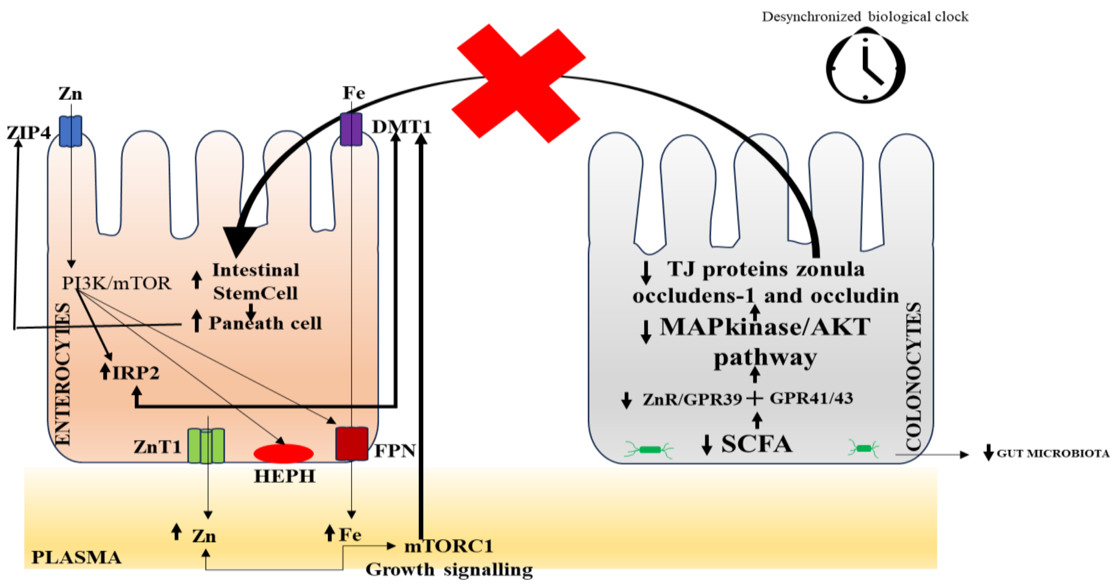

Figure 3. Hypothetical model for effects of desynchronization of circadian rhythm on intestinal zinc and iron absorption.

Conclusion

Complex dynamics of macro and micronutrient deficiencies and intriguing roles of gut microbiota have been discussed in previous studies. However, this paper highlights the facts of circadian rhythms and complex interplays of micronutrients and gut microbiota. The differential regulation of the clock genes based on the light and dark cycle regulates the efficacies of beneficial microbes colonizing at the colonocytes to modulate the absorption kinetics of the micronutrients. Thus, the possible pathway of modulating the expression MAP kinase in deficiency and sufficiency of SCFA could unfold the complex yet essential concepts on the dynamics of the micronutrient, microbiota, and circadian rhythm in the physiological system. Understanding the interplay between circadian rhythms and gut microbiota holds promise for informing interventions to optimize micronutrient absorption and overall health. By elucidating the signaling pathways involved in the modulation of nutrient absorption kinetics, potential strategies for targeted lifestyle modifications or dietary interventions could emerge. In conclusion, further exploration in this field has the potential to not only enhance our understanding of the intricate relationship between micronutrients, gut

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microbiota, and circadian rhythms but also pave the way for practical applications that can positively impact human health.

Conflicts of interest

The authors have declared no conflicts of interest for this article.

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This manuscript is a review article so data sharing is not applicable for this article. No new data were created or analyzed in this manuscript.

Notes on contributors

Arnab Chatterjee & Smita Sahu: writing – review and editing (lead); *Divya Kumari*, *Amit Kumar Banerjee & Shashi Bhushan Kumar:* Writing – original draft, review and editing (supporting); *Virendra Panpatil*: Conceptualization (lead), resources (lead) & supervision (lead).

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