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Pregled
Review

VITAMIN B_{12} AND COLORECTAL CANCER: FRIEND OR FOE? A NARRATIVE REVIEW OF AVAILABLE EVIDENCE

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Purpose: To review the potential relationship between vitamin B_{12} and colorectal cancer, with particular emphasis on its involvement in one-carbon metabolism and epigenetic regulation.

Methods: This narrative review summarises current evidence on the biological mechanisms and epidemiological associations linking vitamin B_{12} status with colorectal cancer risk.

Results: Available evidence indicates a biologically plausible but epidemiologically inconsistent relationship between vitamin B_{12} and colorectal cancer. Studies assessing dietary intake frequently report an inverse association, particularly for rectal cancer, whereas analyses of circulating vitamin B_{12} concentrations yield heterogeneous, and often conflicting findings.

Conclusion: Vitamin B_{12} does not act as an isolated protective factor but as part of a complex metabolic and nutritional system. Although its potential protective role in colorectal carcinogenesis is biologically based, it remains insufficiently confirmed, emphasising the need for further integrated research.

Keywords: CARCINOGENESIS, COLORECTAL CANCER, EPIGENETICS, NUTRITION, ONE-CARBON METABOLISM, VITAMIN B_{12}

1. Introduction

Colorectal cancer (CRC) constitutes a major public health problem globally, owing to its high prevalence and substantial contribution to cancer-related mortality. Despite advances in screening and therapy, the incidence of CRC remains high, especially in developed countries, with a concerning increase among younger age group, highlighting the importance of lifestyle and environmental factors (1-3). Epidemiological evidence consistently identifiesmodifiable lifestyle-related factors such as unhealthy eating habits, sedentary behaviour, obesity, and alcohol consumption as key contributors to CRC risk. Conversely, diets characterised by high intakes of fibre, fruits, and vegetables are associated with a reduced risk (4, 5). These findings are also supported by a substantial number of evidence cases indicating that a substantial proportion of CRC cases is attributable to modifiable lifestyle and dietary factors, highlighting their potential for prevention (6).

Micronutrients involved in one-carbon metabolic pathways receive considerable attention in nutrition due to their importance for DNA synthesis, epigenetic regulation, and genome integrity. Vitamin B_{12} (cobalamin) plays a central role in this system by enabling the conversion of homocysteine to methionine and supporting the production of S-adenosylmethionine (SAM), the universal source of methyl groups (7-9). Since vitamin B_{12} is found almost exclusively in animal-based foods, deficiency may occur in susceptible populations. Elderly individuals and those with absorption disorders are particularly affected, with possible consequences for metabolic and epigenetic processes linked to carcinogenesis (10).

Currently available evidence suggests a biologically plausible but epidemiologically inconsistent association between vitamin B_{12} and CRC. While studies assessing dietary intake more often indicate a potential inverse relationship, particularly for rectal cancer, findings based on circulating vitamin B_{12} concentrations remain heterogeneous and, in some cases, suggest an increased risk of CRC at sustained high levels (11-13).

Despite growing interest in micronutrients involved in one-carbon metabolism, the specific role of vitamin B_{12} in colorectal carcinogenesis remains unclear due to inconsistent epidemiological findings and differences in study design.

This paper aims to examine the potential role of vitamin B_{12} in colorectal

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carcinogenesis, with particular emphasis on its involvement in one-carbon metabolism, epigenetic regulation, and genomic stability.

This narrative review is based on a non-systematic search of the available literature conducted in major scientific databases, including PubMed and Scopus. Relevant studies published in English were identified using combinations of keywords related to "vitamin B_{12}", "colorectal cancer", "one-carbon metabolism", and "epigenetics". The selection of studies was guided by their relevance to the topic, with an emphasis on recent review articles, prospective cohort studies, and mechanistic studies that address underlying biological pathways. Additional relevant publications were identified through the reference lists of selected articles. In accordance with the narrative design of this review, no formal inclusion or exclusion criteria were defined, nor was a standardised systematic search strategy was applied

2. Biological Background of Colorectal Cancer

CRC arises through a slow and biologically complex process characterised by the progressive accumulation of genetic and epigenetic alterations in the epithelial cells of the colon and rectum. In most sporadic cases, malignant transformation follows the classical adenoma-carcinoma pathway. During this sequence, normal mucosa progressively develops into adenomatous precursor lesions. With ongoing molecular damage, these lesions may eventually progress to invasive carcinoma. This stepwise evolution is driven by disruptions in genes that regulate cell-cycle control, cellular differentiation, signal transduction, and genomic stability, including APC, KRAS, BRAF, and TP53. The entire process typically spans more than 10 years (14-18).

While earlier studies primarily focused on the sequence of genetic alterations involved in CRC development (e.g., (17)), more recent research has adopted a more integrative perspective, emphasising the interaction between genetic and epigenetic mechanisms (16, 18). In addition, review articles highlight the heterogeneous nature of CRC and the involvement of multiple signalling pathways (14, 16).

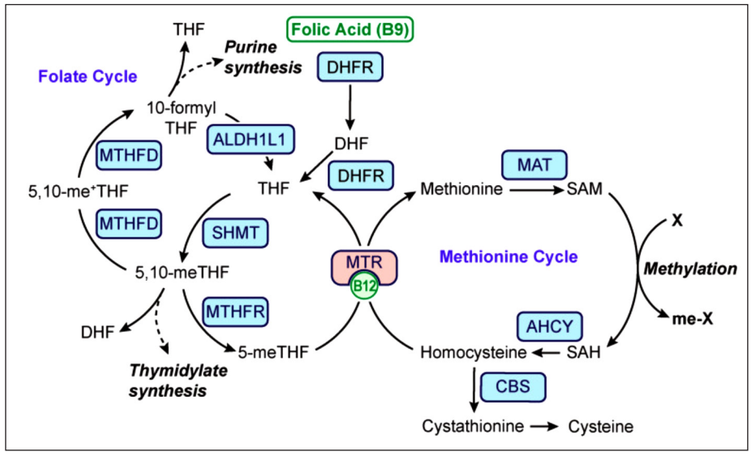

Figure 1.
Schematic representation of one-carbon metabolism, including the folate and methionine cycles. Vitamin B12 acts as a cofactor for methionine synthase, enabling the conversion of homocysteine to methionine and the generation of S-adenosylmethionine (SAM), the universal methyl donor involved in DNA methylation (21).

In addition to chromosomal instability, present in most sporadic cases of CRC, alternative molecular pathways have been recognised in the pathogenesis, including microsatellite instability and epigenetic phenotypes characterised by aberrant DNA methylation. Epigenetic changes, particularly in methylation patterns, are considered early and functionally significant events in carcinogenesis because they lead to the inactivation of tumour suppressor genes and dysregulation of gene expression, often before the appearance of morphologically visible lesions (3, 4, 19, 20).

While earlier studies demonstrated the involvement of DNA methylation in carcinogenesis, more recent studies have highlighted its complex and context-dependent nature, indicating that epigenetic changes may occur during the early stages of tumour formation and be influenced by environmental and dietary factors (20, 24-26).

3. One-Carbon Metabolism and the Role of Vitamin B_{12}

3.1. Folate and Methionine Cycle

It is increasingly recognised that epigenetic regulation represents a key link between environmental factors and the molecular mechanisms of carcinogenesis, with nutrition acting as an important modulating factor, particularly through its influence on metabolic pathways involved in nucleotide synthesis and methylation processes. One-carbon metabolism integrates the folate and methionine cycles and provides methyl groups necessary for DNA synthesis and epigenetic regulation (7, 8). The key components of one-carbon metabolism, including the folate and methionine cycles, are schematically presented in Figure 1.

Disruptions in this system (Figure 1) may impair thymidylate synthesis, increase uracil incorporation into DNA, and lead to DNA strand breaks and chromosomal instability, which are recognised as early events in colorectal carcinogenesis (9, 19). These alterations may contribute to genomic instability and increased susceptibility to malignant transformation.

3.2. Role of Vitamin B_{12} and SAM Synthesis

Vitamin B_{12} (cobalamin) plays a central role in one-carbon metabolism as a cofactor of the enzyme methionine synthase (Figure 1), which catalyses the remethylation of homocysteine to methionine. This reaction is essential for the synthesis of SAM, the universal methyl donor required for DNA and histone methylation. Through this mechanism, vitamin B_{12} indirectly influences epigenetic regulation and contributes to maintaining genomic stability (7, 8). Adequate availability of SAM is crucial for the preservation of normal DNA methylation patterns, which are frequently altered in CRC.

3.3. Methyl-Trap and Genomic Instability

Vitamin B_{12} deficiency leads to the so-called methyl-trap phenomenon, which reducesfolate availability for thymidylate synthesis and increases the likelihood of DNA damage and mutational burden. This provides a biological basis for the hypothesis that long-term disruption of vitamin B_{12} status may affect early stages of colorectal carcinogenesis (9, 22).

In addition, several studies have linked vitamin B_{12} status to the methylation of promoter regions of genes such as MLH1 and MGMT, which are involved in DNA repair and cell cycle regulation, further supporting a potential epigenetic mechanism of vitamin B_{12} action (19, 22, 23). Such alterations may contribute to impaired DNA repair capacity and promote tumour development.

4. Epigenetic Mechanisms in Colorectal Carcinogenesis

4.1. DNA Methylation and Gene Regulation

Epigenetic alterations, particularly changes in DNA methylation patterns, represent early and functionally significant events in colorectal carcinogenesis. Aberrant DNA methylation can lead to the silencing of tumour suppressor genes and dysregulation of gene expression, often occurring before the development of morphologically detectable lesions (19, 24-26).

DNA methylation is primarily mediated by the availability of methyl groups derived from one-carbon metabolism, highlighting the importance of metabolic regulation in maintaining genomic stability. Disruptions in methyl group availability may result in global DNA hypomethylation, which is associated with genomic instability, and gene-specific hypermethylation, leading to transcriptional silencing of key regulatory genes (24-26).

These epigenetic alterations are increasingly recognised as dynamic and reversible processes influenced by environmental and nutritional factors, further supporting their role as a mechanistic link between diet and colorectal carcinogenesis.

4.2. Tumour Suppressor Genes (MLH1, MGMT)

Promoter hypermethylation of tumour suppressor genes such as MLH1 and MGMT plays a critical role in CRC development. MLH1 is involved in DNA mismatch repair, while MGMT is responsible for repairing DNA damage caused by alkylating agents. Epigenetic silencing of these genes may result in impaired DNA repair mechanisms, accumulation of mutations, and increased cancer risk (27, 28).

MLH1 promoter hypermethylation is strongly associated with microsatellite instability, a well-established molecular subtype of CRC, while MGMT silencing has been linked to increased mutation burden and tumour progression (27-29).

Several studies have linked vitamin B_{12} status to the methylation of promoter regions of tumour suppressor genes, such as MLH1 and MGMT, suggesting a potential interaction between nutritional status and gene regulation (19, 22, 23). This further supports the concept that micronutrient availability may influence key epigenetic mechanisms involved in colorectal carcinogenesis.

4.3. Nutritional Modulation of Epigenetics

Nutritional factors, particularly micronutrients involved in one-carbon metabolism, play an important role in modulating epigenetic processes. Vitamins, such as folate and vitamin B_{12}, contribute to the regulation of DNA methylation by supporting methyl group metabolism, thereby influencing gene expression and genomic stability (7-9).

Disruptions in nutrient availability may alter DNA methylation patterns and lead to epigenetic dysregulation, which has been implicated in the early stages of colorectal carcinogenesis. These findings support the concept that diet is a key environmental factor capable of influencing epigenetic mechanisms involved in cancer development. In this context, vitamin B_{12} does not act in isolation but rather as part of a complex metabolic network, interacting with other nutrients involved in one-carbon metabolism. Such interactions may be particularly relevant in determining overall methylation capacity and susceptibility to epigenetic alterations associated with colorectal cancer.

5. Epidemiological Evidence on Vitamin B_{12} and Colorectal Cancer

Observational studies based on the assessment of dietary vitamin B_{12} intake often suggest a potential inverse association with colorectal cancer risk, particularly for rectal cancer (11, 30-32). These findings are consistent with the hypothesis that adequate functioning of one-carbon metabolism may contribute to genomic stability and reduced epigenetic dysregulation. However, consistent associations for overall CRC are lacking, indicating possible biological and anatomical heterogeneity of the disease. Moreover, dietary assessment methods are prone to measurement error and residual confounding, particularly due to correlated intake of other nutrients involved in one-carbon metabolism, such as folate, which complicates the attribution of independent effects to vitamin B_{12}.

In contrast, studies evaluating circulating vitamin B_{12} concentrations report inconsistent and, in some cases, opposing results. Some analyses, including Mendelian randomisation studies, suggest a potential association between persistently elevated vitamin B_{12} levels and increased cancer risk (12, 13, 33). These findings are often interpreted in the context of reverse causation or as markers of underlying pathological processes rather than evidence of a direct harmful effect of vitamin B_{12}. Elevated circulating vitamin B_{12} concentrations have been associated with liver dysfunction, inflammation, and malignancy-related metabolic alterations, further complicating causal interpretation.

An additional challenge in interpreting epidemiological data relates to variability in vitamin B_{12} status across populations. Differences in dietary intake, absorption, and metabolic factors may contribute to heterogeneous exposure levels, further complicating the interpretation of associations between vitamin B_{12} and CRC risk. This heterogeneity is further amplified by differences in study design, population characteristics, and biomarker selection, which may partially explain the inconsistencies observed across epidemiological studies.

6. Discussion

Our findings highlight a biologically plausible but epidemiologically inconsistent relationship between vitamin B_{12} and CRC. The potential protective role of vitamin B_{12} is supported by its involvement in one-carbon metabolism, nucleotide synthesis, and epigenetic regulation, which are critical processes in the early stages of colorectal carcinogenesis (7-9, 11, 15). However, these conclusions should be interpreted with caution, as the available evidence is subject to several important limitations.

For example, Dahlin et al. conducted a nested case-control study investigating the association between circulating vitamin B_{12} concentrations and CRC risk (11). Although the study suggested association between plasma vitamin B_{12} levels and CRC, the findings were inconsistent. This may be explained by several methodological limitations, including a relatively small number of cases, which may have reduced statistical power, and the use of a single-time biomarker measurement that does not adequately reflect long-term vitamin B_{12} status. In addition, reverse causation cannot be excluded, as elevated circulating vitamin B_{12} levels may be influenced by underlying pathological conditions.

Similarly, mechanistic evidence, such as the study by Brunaud et al., supports the biological plausibility of vitamin B_{12} involvement in carcinogenesis (8). This experimental animal study demonstrated that vitamin B_{12} and folate deficiency can lead to alterations in DNA methylation. However, these findings are based on animal models, which may not fully reflect human physiology. Furthermore, the experimental conditions, including nutrient doses, may not correspond to physiologically relevant levels observed in humans, thereby limiting their direct clinical applicability.

Future studies should incorporate longitudinal designs with repeated biomarker measurements to better capture long-term vitamin B_{12} status, as well as translational research conducted in human populations using physiologically relevant exposure levels. Consistent with these considerations, epidemiological evidence remains heterogeneous and difficult to interpret. Studies assessing dietary vitamin B_{12} intake more frequently suggest a potential protective effect, particularly for rectal cancer. In contrast, studies based on circulating vitamin B_{12} concentrations often report null or even positive associations with cancer risk (11, 30-33). This discrepancy likely reflects fundamental methodological differences, including measurement limitations, confounded by other dietary factors, and the complex biological interpretation of circulating vitamin B_{12} levels. Circulating vitamin B_{12} may not represent a reliable marker of nutritional status in all contexts, as elevated concentrations can be associated with underlying pathological conditions such as liver disease, inflammation, or malignancy. This raises the possibility that observed positive associations between high vitamin B_{12} levels and cancer risk may reflect reverse causation rather than a direct causal effect (33). While in general, higher adherence to the World Cancer Research Fund/American Institute for Cancer Research Cancer Prevention Recommendations is linked to a lower risk of CRC, vitamin B_{12} is not particularly emphasised as the key nutrient with protective effect (34). Our findings, however, indicate that dietary diversity, specifically the one related to regional dietary characteristics, could play an important role, along with the contribution of particular food groups to the total dietary vitamin B_{12} intake (35, 36).

Another important consideration is the interaction between vitamin B_{12} and other nutrients involved in one-carbon metabolism, particularly folate. The biological effects of vitamin B_{12} are unlikely to occur in isolation but rather depend on the overall nutritional and metabolic context, as highlighted in systematic reviews of one-carbon metabolism (9).

Furthermore, epigenetic mechanisms provide a plausible link between vitamin B_{12} status and colorectal carcinogenesis. Evidence suggests that vitamin B_{12} may influence DNA methylation patterns, including the regulation of genes involved in DNA repair and cell cycle control, such as MLH1 and MGMT (19, 23).

Taken together, these findings suggest that vitamin B_{12} should not be interpreted as an independent protective or risk factor, but rather as part of a complex metabolic and epigenetic network. Future research should focus on integrative approaches that combine dietary assessment, biomarker data, and epigenetic profiling to better clarify the role of vitamin B_{12} in colorectal carcinogenesis.

This review has several limitations. As a narrative review, it is subject to potential selection bias and does not follow a systematic review methodology. Furthermore, heterogeneity across studies in terms of design, population characteristics, and exposure assessment limits the comparability and generalizability of the findings. Despite these limitations, this review has several important strengths. It provides an integrative perspective by combining evidence from epidemiological, mechanistic, and epigenetic studies, thereby allowing for a more comprehensive understanding of the potential role of vitamin B_{12} in colorectal carcinogenesis. In addition, particular emphasis is placed on the interaction between vitamin B_{12} and one-carbon metabolism, highlighting its context-dependent effects rather than considering it as an isolated factor. The present paper highlights the need for more methodologically rigorous approaches, particularly systematic reviews and well-designed prospective studies. Further research focusing on specific populations may contribute to a better understanding of context-dependent effects and help inform targeted prevention strategies. Overall, this review provides a foundation for future research to clarify the complex relationship between vitamin B_{12} and CRC.

7. Conclusion

Vitamin B_{12} plays an important role in one-carbon metabolism, DNA synthesis, and epigenetic regulation, processes that are essential for maintaining genomic stability and may be involved in the early stages of colorectal carcinogenesis. While biological mechanisms support a potential protective role of vitamin B_{12}, epidemiological evidence remains inconsistent and does not allow for definitive conclusions. Current findings suggest that vitamin B_{12} should not be considered an independent protective factor, but rather a part of the complex metabolic and nutritional network interacting with other dietary and environmental influences. The observed discrepancies between dietary intake and circulating vitamin B_{12} concentrations in relation to CRC risk further highlight the complexity of its role in CRC pathology. Future research should focus on integrative approaches combining dietary assessment, biomarkers, and epigenetic data to better clarify the role of vitamin B_{12} in colorectal carcinogenesis and to identify conditions under which its potential protective effects may be relevant.

Abbreviations:

AHCY - Adenosylhomocysteinase
ALDH1L1 - Aldehyde Dehydrogenase 1 Family Member L1
APC - Adenomatous Polyposis Coli
BRAF - proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene
CBS - Cystathionine-β-synthase
CRC - Colorectal Cancer
DHFR - Dihydrofolate reductase
DNA - Deoxyribonucleic acid
KRAS - Kirsten Rat Sarcoma Viral Oncogene Homologue
MAT - Methionine Adenosyltransferase
MGMT - O(6)-methylguanine-DNA methyltransferase
MLH1 - MutL protein homolog 1
MTHFD - Methylenetetrahydrofolate dehydrogenase
SAM - S-adenosylmethionine
SHMT - Serine hydroxymethyltransferase
TP53 - Tumor Protein p53

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Sažetak

VITAMIN B_{12} I KOLOREKTALNI RAK: PRIJATELJ ILI NEPRIJATELJ? NARATIVNI PREGLED DOSTUPNIH DOKAZA

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Cilj ovog rada bio je istražiti potencijalnu povezanost između vitamina B_{12} i kolorektalnog karcinoma, s posebnim naglaskom na njegovu ulogu u metabolizmu jednougljičnih skupina i epigenetskoj regulaciji. Ovaj narativni pregled sažima dostupne dokaze o biološkim mehanizmima i epidemiološkim povezanostima između statusa vitamina B_{12} i rizika od kolorektalnog karcinoma. Dostupni dokazi upućuju na biološki utemeljenu, ali epidemiološki nedosljednu povezanost između vitamina B_{12} i kolorektalnog karcinoma. Istraživanja temeljena na procjeni prehrambenog unosa često ukazuju na moguću inverznu povezanost, osobito za karcinom rektuma, dok analize koncentracija vitamina B_{12} u cirkulaciji pokazuju heterogene i često proturječne rezultate. Vitamin B_{12} ne djeluje kao izolirani zaštitni čimbenik, već kao dio složenog metaboličkog i nutritivnog sustava. Iako je njegov potencijalni zaštitni učinak u kolorektalnoj karcinogenezi biološki utemeljen, još uvijek nije dovoljno potvrđen, što naglašava potrebu za daljnjim integriranim istraživanjima.

Ključne riječi: EPIGENETIKA, KARCINOGENEZA, KOLOREKTALNI KARCINOM, METABOLIZAM JEDNOUGLJIČNIH SKUPINA, PREHRANA, VITAMIN B_{12}

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