**Review Article****Mechanistic links between dietary protein and colorectal cancer: a mini review**

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Protein, an essential and indispensable component of our diet, provides amino acids for the development, growth, and maintenance of human body. There is growing concern that protein intake from certain sources and dietary patterns may be a triggering factor for colorectal cancer (CRC). However, the link between dietary protein intake and CRC remains unclear, and the researchers are working to unravel the connection and its implications. Although specific reports showed red and processed meat linked with an increased risk of CRC, several recent studies exhibited CRC inversely tied with certain types of amino acid intake. Accumulating data indicate that CRC development is multifactorial, including dietary and lifestyle factors, environmental factors, and genetic factors. Moreover, the development and progression of CRC depend on several disruptive molecular pathways. These findings collectively suggest that protein source, dietary diversity, and food preparation methods are more meaningful determinants of CRC risk than protein intake per se. A balanced diet incorporating varied protein sources, along with fiber, vitamins, and minerals, remains the most evidence-supported strategy for CRC prevention. This article argues with the recent conceivable theories about CRC development, progression and its relationship with dietary protein and synthesizes current evidence on the relationship between dietary protein intake and CRC risk concluding that no direct causal link exists between overall protein consumption and CRC development.

Introduction

Proteins are macronutrients which consist of amino acids and are the important building blocks for the growth and development of our body. Living bodies are constantly replacing old proteins with new ones to remain healthy. Proteins consist of different types of amino acids. From a nutritional point of view, 4 calories of energy obtained from each gram of protein and thus for a healthy adult, the requirement of a daily protein intake is 0.8 gm per kilogram of body weight from complete, incomplete and complementary protein sources which contains both

essential and non-essential amino acids and are required for the optimal muscle maintenance (Mayo Clinic Health System, 2025; Life's Building Blocks, 2025).

Colorectal cancer (CRC) has gained much attention recently because it is one of the most diagnosed cancers in the world. It is ranked third in the growing incidence of 1.9 million new CRC cases per year and second by the increased mortality rate (Sung et al., 2021). The most increased occurrence is seen in the developed countries and is predicted to increase by 2.2

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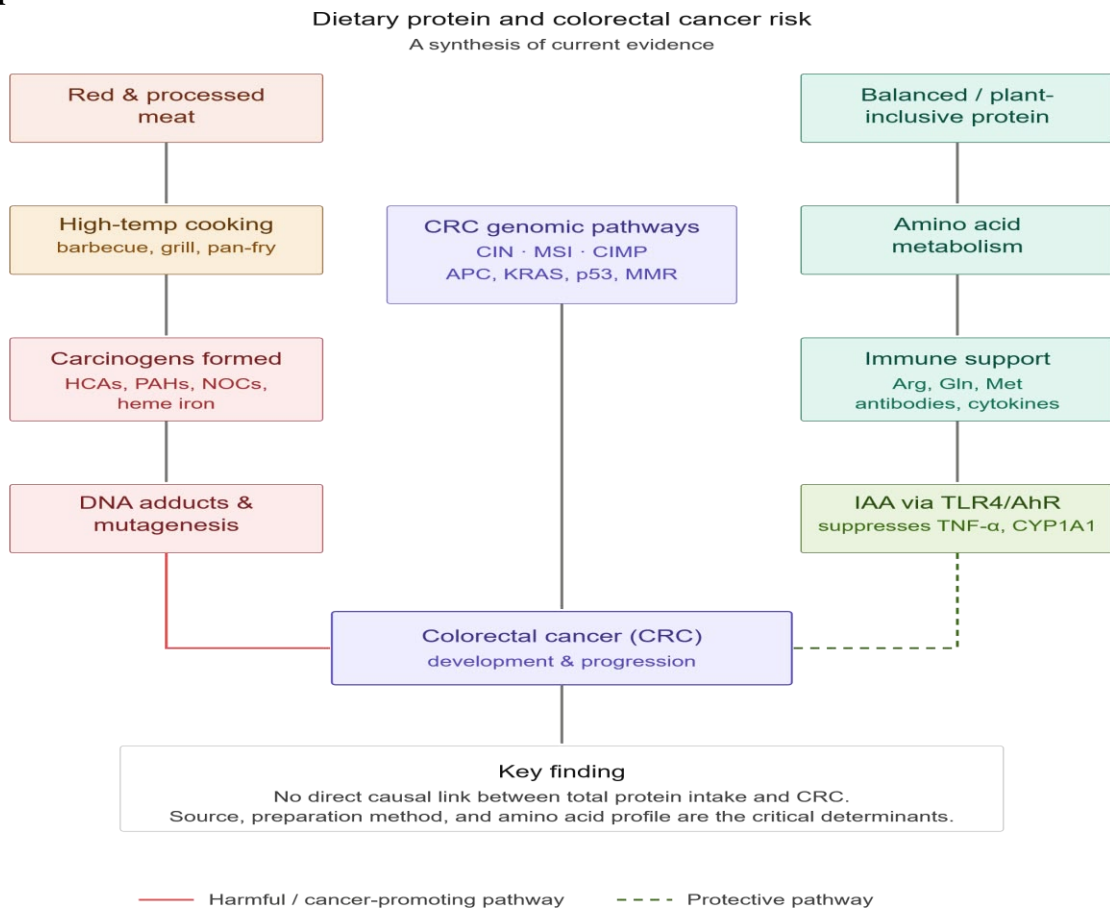
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million new cases yearly by 2030 in developing countries (Arnold et al., 2017). Out of several factors, researchers have shown the link of socioeconomic status, sedentary lifestyle and low fiber intake, genomic association with BMI, *HAS2* and *SMAD7* genes mutation, alkylating DNA mutations of KRAS and APC through higher amount of heme intake and long-term aspirin therapy. In addition to these, recent publication shows that physical activity and fitness is somehow associated with chemotherapeutic responses with certain types of cancer (Summary of the Third Expert Report, 2018). Among the dietary factors implicated in CRC development, the excessive consumption of red and processed meat has attracted considerable epidemiological and experimental scrutiny. A comprehensive meta-analysis of prospective studies confirmed that high intake of red and processed

meats is significantly associated with an elevated risk of colorectal, colon, and rectal cancers reinforcing current dietary recommendations that advocate limiting such consumption as part of cancer prevention strategies (Ungvari et al., 2025). Furthermore, a large-scale study utilizing polygenic risk scoring demonstrated that red and processed meat intake independently compounds CRC risk beyond genetic predisposition alone, suggesting a direct dietary contribution to colorectal carcinogenesis (Fu et al., 2024). Nonetheless, the carcinogenic potential of processed meat is not attributable solely to its protein content; rather, it is substantially mediated by harmful chemical compounds generated during thermal processing. Among these, heterocyclic compounds like polycyclic aromatic hydrocarbons (PAHs) formed when fats from meat drip onto open flames during grilling or barbecuing and

Graphical Abstract



undergo metabolic activation of certain enzymes, leading to the formation of highly reactive intermediates that form covalent DNA adducts in colonic epithelial cells, thereby inducing oncogenic mutations and initiating colorectal carcinogenesis (Bulanda and Janoszka, 2022). Moreover, experimental evidence demonstrates that the inflammatory mediator TNF- α , which is elevated in the CRC tumor microenvironment, synergistically amplifies PAH-induced DNA damage in colon cancer cells through modulation of AhR-dependent CYP expression, further linking dietary carcinogen exposure to the pro-inflammatory milieu of CRC progression (Alotaibi et al., 2021). Collectively, these findings underscore that the risk associated with excessive protein consumption from processed meat sources is primarily driven by the byproducts of high-temperature food preparation rather than by protein intake itself, highlighting the critical importance of both food source selection and cooking method in CRC risk reduction. However, no sharp clues for the advancement of CRC by protein intake can be portrayed from those publications. As a matter of fact, this review article will explain the research findings, scientific mechanisms behind the development and progression of CRC and their link to any type of protein intake.

Common risk factors associated with CRC

Several studies revealed that both lifestyle and genetic factors might play an important role in the development and progression of CRC. Lifestyle factors, for example alcohol consumption, cigarette smoking, obesity, etc., dietary factors such as intake of red and processed meat and disease status like diabetes, insulin resistance, inflammatory bowel disease, coronary heart disease and other infectious diseases are all considered crucial factors for the increased risk of CRC.

Concerns regarding the association between dietary protein intake and CRC

Multiple studies have investigated the potential link between protein intake with CRC. A study by

Bradbury et al. found that increased consumption of red and processed meat was positively linked with an elevated CRC risk. They concluded that people who ate over 100 g of red and processed meat each day challenged a 17% greater likelihood of developing CRC than those who consumed below 20 g each day. However, the specific mechanism was not portrayed in the literature (Bradbury et al., 2020). Similarly, Zhao and his group reported that a substantial consumption of animal protein, especially from red and processed meats, was consistently linked to increased risk of CRC. The group also suggested that components such as heme iron or heterocyclic amines (HCA) present in processed meats might contribute to this association (Zhao et al., 2017); nonetheless, their hypothesis lacks a conclusive biological pathway. Furthermore, another study reported that replacing animal protein (particularly red meat) with secondary plant proteins is associated with a reduced risk of CRC, implying that the type of protein consumed could influence CRC risk, even so, the study did not provide any conclusive mechanism and emphasized the importance of further research (Liao et al., 2019). Elsewhere, the established association with red and processed meat, emerging evidence suggests that the overall quality and source of dietary protein rather than its quantity alone might be a more meaningful determinant of CRC risk. A large prospective analysis of the UK Biobank cohort, encompassing over 114,000 participants followed for a median of 9.4 years, reported that higher intake of dairy protein and protein from milk was inversely associated with CRC incidence, suggesting a potential protective effect of certain animal protein sources that stands in contrast to the risk attributed to red and processed meat (Watling et al., 2023). Similarly, a recent population-based prospective study demonstrated that adherence to a diet characterized by higher protein quality defined by a favorable balance of essential amino acids and protein source diversity was significantly associated with a reduced risk of CRC, reinforcing the concept that protein quality may be more clinically relevant than total protein quantity

(Feng et al., 2025). Therefore, the aim of our review is to unveil the real mechanism of CRC progression and find out any possible association between dietary protein intake and CRC.

Molecular mechanism of CRC development and progression

The pathogenesis and advancement of CRC is represented as a complex and multi-stage process from the initiation to metastasis and involves several different pathways. The irrevocable modification of genomic material has been showcased in human colonic mucosa initially, and such persistent DNA mutations might play a significant role in the formation of adenomas and particularly promoting them to the metastasis phase by any additional genetic and/or epigenetic modifications (Keum and Giovannucci, 2019). The three most commonly involved genomic disruptive pathways that lead to CRC development are chromosomal instability (CIN), microsatellite instability (MSI), and the CpG island methylator phenotype (CIMP) pathway (Colussi et al., 2013; Pierantoni et al., 2024; Koveitypour et al., 2019). The CIN is characterized by massive changes

in structural as well as copy number chromosomal abnormalities. The crucial turning point of CIN pathways is the activation of the *Wnt* signaling pathway due to the mutation of the adenomatous polyposis coli or APC gene. Mutations in APC, which act as a negative regulator of the *Wnt* program, resulted in the accumulation and translocation of β -catenin in the nucleus and subsequent binding with the transcription factors, leading to the activation of TCF targets and thus inducing cell proliferation and development of CRC [Fig 1]. Other factors that are directly or indirectly involved in the upregulation of β -catenin and its accumulation in the nucleus are *CKD8* (Cyclin-dependent Kinase 8), Cyclin D1 (*CCND1*), and Notch pathways. Following the development of adenomatosis, continuation of CRC progression mainly occurs through the activation of the Ras signaling pathway by *KRAS* protein mutation, which leads to the activation of a series of other molecular pathways. Later, the mutation and loss of function of p53 impacts in the final stages of CRC advancement. Moreover, the evidence suggested that the cross-talk between p53 and Cyclooxygenase-2 (*COX-2*) promotes inflammation and thus CRC progression.

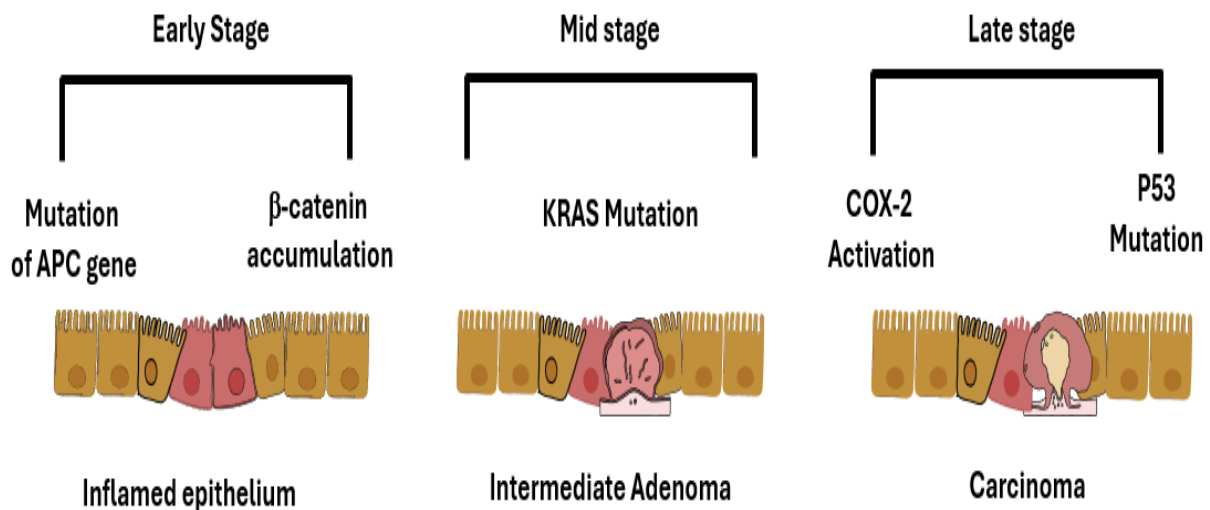


Fig. 1. Key Molecular Events in Chromosomal Instability towards CRC Progression.

On the other hand, MSI occurs due to the insertion or deletion mutation in the repetitive sequence of the microsatellite region, resulting in the inactivation of the part of the DNA mismatch repair system (MMR), such as MLH1 and MSH2 genes (Colussi et al., 2013). Finally, the CIMP pathway, also known as the Serrated pathway, is caused by hypermethylation of dinucleotide cytosine-guanine sequences or CpG islands, accountable for the regulation of cell cycle, DNA repair, and apoptosis. Thus, this epigenetic modification or silencing of particular tumor suppressor genes leads to uncontrolled cell proliferation, and development and progression of carcinogenesis (Myöhänen et al., 1998).

Recently cytokine-mediated inflammatory processes, mainly tumor necrosis factor alpha (TNF- α), are expressed highly in CRC cells and are linked to CRC metastasis and advanced CRC progression (Al Obeed et al., 2014). In addition, phase II metabolizing enzymes, namely cytochrome P450s, are shown to activate procarcinogens like PAH. The mutation of CYP1A1, one of the members of the cytochrome P450 multigene superfamily, leads to increased risk of CRC development (Gil et al., 2014; Xu and Wei, 2015).

Involvement of protein in the molecular pathways of CRC

Proteins are essential in the molecular pathways that promote CRC development, influencing key functions like cell growth, apoptosis, and the spread of cancer cells (Koveitypour et al., 2019; Huang et al., 2022). For instance, recent research found that the p53 tumor-suppressing proteins are commonly mutated in CRC cell death, thus enhancing CRC progression (Frum and Grossman, 2014). It stimulates p21 (WAF1), a CDK suppressor that hinders the progression from the G1 to S phase, while simultaneously promoting programmed cell death by directly inducing pro-apoptotic proteins like Bcl-2, Noxa, and PUMA, and by triggering the caspase-8 cascade through activation of receptors such as DR5, Fas, or PIDD. However, no studies have associated dietary protein consumption with exaggerating the CRC through the p53 pathway. Similarly, KRAS mutations are also significant to CRC proliferation, contributing to treatment

impediment, greatly hindering treatment strategies in affected individuals (Takeda et al., 2025). These mutations lead to continuous activation of cancer-promoting pathways like PI3K/AKT and MAPK/ERK (Takeda et al., 2025), thereby promoting tumor progression and undesired treatment outcomes (Takeda et al., 2025; Lavoie et al., 2020), although no research has proved that KRAS mutation is linked to protein diets which might promote CRC advancement (El Asri et al., 2020), thus necessitating to reveal the association between dietary protein and CRC. Furthermore, a study by Huang et al. found a positive link between Interleukin-6 (IL-6) and CRC. It activates the JAK2/STAT3 signaling cascade, which contributes to CRC initiation and proliferation (Huang and Yang 2022). However, there are inconsistent reports on whether dietary protein intake exacerbates or suppresses the IL-6/JAK/STAT3 signaling cascade in CRC progression (Gholamalizadeh et al., 2024).

Current evidence on the relationship between dietary protein intake and development of CRC

A good number of studies have evaluated the association between protein consumption and CRC risk and found no significant link. A meta-analysis conducted by Lai et al. concluded that there is no significant positive relationship between protein intake and CRC and recommended additional research with larger sample size with precise amount of dietary protein intake to validate this finding (Lai et al., 2017). In addition, the European Prospective Investigation into Cancer and Nutrition (EPIC), one of the largest cohort studies, demonstrate that there is an inverse relationship between dietary protein intake and CRC development; however, the study did not explore the exact mechanisms (Papadimitriou et al., 2022).

Food habits and cooking processes: in the prevention of CRC development Non-digestible fiber intake alongside dietary protein

Consumption of non-digestible dietary fiber alongside protein-rich foods is increasingly recognized as a critical dietary strategy for CRC prevention. Dietary fiber, particularly soluble and fermentable forms such

as inulin and pectin, serve as primary substrates for colonic microbiota, stimulating the production of short-chain fatty acids (SCFAs), particularly butyrate, propionate, and acetate and plays a central role in CRC chemoprevention by inhibiting histone deacetylase (HDAC) activity, inducing cancer cell apoptosis, suppressing colonic inflammation, and maintaining epithelial barrier integrity (Maiuolo et al., 2024). Furthermore, a high-fiber diet usually accelerates intestinal transit time, thereby reducing prolonged mucosal exposure to protein fermentation byproducts such as ammonia and secondary bile acids, which are recognized promoters of colorectal carcinogenesis (Appunni et al., 2021). These illustrate the importance of fiber consumption as complementary dietary components for the prevention of CRC development.

Bioactive peptides as a source of limiting amino acids

Bioactive peptides, the short protein fragments of two to twenty amino acids released during gastrointestinal digestion or fermentation, can supply conditionally essential amino acids including glutamine, arginine, and methionine which are critical for intestinal epithelial repair, immune cell function, and gut barrier maintenance. Besides, bioactive peptides derived from legumes, marine organisms, and fermented dairy products have demonstrated direct anticancer activity in CRC models including the inhibition of cell proliferation, induction of apoptosis via caspase-3 activation, and suppression of tumor angiogenesis (Ghadiri et al., 2024). Collectively, bioactive peptides represent an emerging dietary source of limiting amino acids and a promising avenue for CRC prevention.

Spicy food and cooking conditions- in the CRC risk assessment

The use of culinary spices in food preparation and the methods by which protein-rich foods are cooked represent significant, yet underappreciated, modulators of CRC risk. Certain bioactive compounds found in commonly used spices, such as curcumin from turmeric and capsaicin from chili peppers have demonstrated anti-inflammatory and anti-tumor properties in preclinical studies, suggesting that spiced

food preparations may confer a degree of protection against colorectal carcinogenesis (Aggarwal and Harikumar, 2009). However, excessive consumption of highly spiced or pickled foods has been associated with gastrointestinal mucosal irritation which may indirectly contribute to inflammatory conditions of the colon.

On the other hand, high-temperature processing methods of red meat, such as barbecuing, grilling, and pan-frying, is associated with an increased risk of CRC through the formation of numerous carcinogenic compounds (Hur et al., 2019). Some of the carcinogens include N-nitroso chemicals (NOCs), polycyclic aromatic hydrocarbons (PAHs), heterocyclic amines (HCAs), and bioactive heme iron (Hur et al., 2019; Zouiouich et al., 2025; Miller et al., 2013). Heterocyclic amines (HCA) are produced when compounds such as amino acids, creatine/creatinine, and sugar found in the muscle tissues undergo chemical reactions at high temperatures above 150°C (Miller et al., 2013; Chemicals in Meat Cooked at High Temperatures and Cancer Risk, 2018; Helmus et al., 2013). Commonly formed HCA include PhIP, MeIQx, and DiMeIQx, which are activated through the enzyme CYP450 (specifically CYP1A2) into reactive byproducts that bind to the DNA to produce complexes on the epithelial cells of the colon (Potera, 2016; Jian et al., 2019). A study found that polyaromatic amines, including benzo[a]pyrene, are produced when fats from meat fall onto heated flames, producing smoke that covers the meat surface (Bouvard et al., 2015). These substances act as ligands for aryl hydrocarbon receptors (AhR) triggering the activation of bioactive enzymes such as CYP1B1, CST, which in turn, produce DNA reactive PAH with mutagenic potential (Casella et al., 2018). Altogether, these metabolic, genetic, and chemical pathways support the notion of increased risk of developing CRC by red meat processed at high temperature. However, other cooking methods have not been linked to increased risk of CRC.

Amino acids boost the immune system

Amino acids serve as important substrates and generate numerous byproducts in various cellular processes. Key amino acids involved in tumor metabolism and immunity include tryptophan,

arginine, and glutamate (Zhu et al., 2025; Wei et al., 2021; Ribeiro Franco et al., 2020). Dietary tryptophan, an essential amino acid, is broken down through the kynurenine pathway into immunologically active metabolites, making this metabolic route a promising focus for immunotherapy (Santhanam et al., 2016; Thaker et al., 2013; Ferdinande et al., 2012). The enzyme, indoleamine 2,3-dioxygenase 1 (IDO1) initiates this pathway and is typically overexpressed in CRC (Santhanam et al., 2016). According to a study by Peyraud et al., the increased kynurenine concentrations within the colorectal tumor microenvironment inhibit the function of cytotoxic T cells, which facilitates immune escape (Prendergast et al., 2014). Whereas disrupting this pathway can reinstate effective anti-tumor immune activity (Peyraud et al., 2022). Similarly, a study by Wyatt et al. describes how tryptophan metabolites produced in the gut microbes, such as indoles, affect intestinal immune function by regulating the equilibrium between anti-inflammatory regulatory T cells and pro-inflammatory T cell populations (Wyatt and Greathouse, 2021). In addition to tryptophan, other amino acids such as methionine, arginine, and glutamine also support the growth and activities of macrophages and lymphocytes (Zhu et al., 2025; Ma et al., 2022). These amino acids from protein consumption are key in producing antibodies, cytokines, and other immune factors necessary for detecting and destroying early-stage cancer cells. Collectively, these findings indicate that diets rich in amino acids can trigger the immune system monitoring mechanism helping to minimize the risk of CRC progression.

Recent findings on reduction of inflammation by the amino acid derivative

Recently, a group of researchers demonstrate that the amino acid derivative, more specifically the tryptophan metabolite indole-3-acetic acid (IAA), not only binds with the AhR but also with the toll-like receptor-4 (TLR4) and can modulate the expression of certain genes reducing the inflammation of the colon. The molecular pathways involved in this mechanism start

by the gut microbiota. Gut microbiomes convert tryptophan, an essential amino acid, to its intermediate metabolite IAA that directly suppresses the TNF- α . Moreover, it can also act as a ligand for TLR4 and inhibit the expression of CYP1A1 through JNK pathway (Chowdhury et al., 2021a; Chowdhury et al., 2021b). This finding justifies the possibility of suppression of CRC by protein diet.

Conclusion

In conclusion, we suggest that eating adequate protein is important for performing daily activities and muscle building, as well as, to support the immune function. On the other hand, increased risk of CRC might result from a combination of factors including lifestyle, food habits precisely the processing method of proteins and other physicochemical and genetic determinants. Based on the several contemporary evidence, our observation is that there is no direct relationship between increased consumption of proteins and CRC development. However, a balanced diet with different types of complete and incomplete proteins along with vitamins, minerals, fibers, and carbohydrates is the best way to prevent most life-style diseases such as cancers, diabetes, and hypertension.

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Data Availability Statement

All data are included in the manuscript.

Author Contribution

MMIC: Conceptualization, Methodology, Formal Analysis, Investigation, Resources, Data Curation, Writing- Original Draft; FA: Methodology, Formal Analysis, Data Curation, Writing- Original Draft; RM: Validation, Writing- Reviews & Editing, Supervision, Project Administration; NK: Formal Analysis, Investigation, Data Curation, Writing- Original Draft; HMR: Conceptualization, Validation, Formal Analysis, Writing- Reviews & Editing, Supervision, Project Administration.

Conflict of Interest

The authors declare that there is no conflict of interest.

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