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Smoking As A Protective Factor for Ulcerative Colitis: A Mini-Review

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1. Abstract

1.1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory condition of the colon characterized by continuous inflammation starting in the rectum. UC predominantly affects populations in Western countries, though incidence is rising in previously low-risk areas. Genetic, environmental, and dietary factors contribute to UC susceptibility, with smoking paradoxically acting as a protective factor.

1.2. Methods

This mini-review explores the current understanding of the mechanisms by which smoking, and specifically nicotine, provides protection against UC development and progression.

1.3. Results

Nicotine modulates immune responses in UC by inhibiting mucosal addressin cell adhesion molecule-1 (MAdCAM-1) expression and NLRP3 inflammasome assembly, reducing leukocyte recruitment and pro-inflammatory cytokine production. Smoking also alters gut microbiota, potentially restoring balance and contributing to its protective effects.

1.4. Conclusion

Despite its protective role in UC, smoking poses significant health risks, necessitating the development of alternative therapies that replicate these effects without harmful consequences. Future research should focus on nicotine-based treatments and immunomodulatory therapies as safer management options for UC patients.

2. Introduction

Ulcerative colitis (UC) is a chronic inflammatory condition of the colon, characterized by continuous inflammation and ulceration of the mucosal layer, starting in the rectum and extending proximally to varying extents throughout the colon [1]. Unlike Crohn's disease, which can affect any part of the gastrointestinal tract and involves deeper layers of the bowel wall, UC is restricted to the colon and affects only the innermost lining [1,2]. UC predominantly affects populations in Western countries, with the highest prevalence seen in North America and Northern Europe3. Recent epidemiological trends indicate a rise in UC incidence in regions historically considered low-risk, such as Asia, South America, and Eastern Europe, suggesting that environmental and lifestyle changes are contributing to the increasing burden of disease globally [1-3]. The age of onset typically peaks between 15 and 30 years, with a smaller second peak occurring in individuals over 60 years of age 3. Although UC affects men and women equally, there is evidence that certain ethnic groups, particularly those of European descent, may be at higher risk [3].

The chronic nature of UC, requiring lifelong management, places a significant burden on healthcare systems due to frequent hospitalizations, surgeries, and long-term medication use, impacting patient quality of life and contributing to economic costs both directly (medical care) and indirectly (lost productivity) [1-4].

The development of UC is influenced by a combination of genetic, environmental, and immunological factors [3,4]. A strong genetic predisposition is evident, as individuals with a family history of inflammatory bowel disease (IBD) are at increased risk4. Certain genes, particularly those related to immune function and gut barrier integrity, have been implicated in UC susceptibility [4]. Environmental factors also play a significant role; urban living and higher socioeconomic status are associated with a greater risk, possibly due to the hygiene hypothesis, which suggests that reduced micro-

bial exposure in cleaner environments can lead to an immune system that overreacts to harmless stimuli4. Additionally, antibiotic use in early life has been linked to dysbiosis, or an imbalance in the gut microbiome, which may contribute to UC development4. Diet is another important factor, with high intake of processed foods, saturated fats, and low dietary fiber potentially increasing susceptibility [2-4]. Interestingly, smoking appears to be a protective factor against UC1-4. Current smokers have a lower risk of developing the disease, and nicotine is thought to play a role in modulating the immune response and altering the gut microbiota [1-4]. However, former smokers exhibit an increased risk compared to those who have never smoked, indicating that smoking cessation may trigger disease onset in predisposed individuals [1-4]. Therefore, this research was designed aiming to promote a mini-review in literature in order to describe the mechanisms by which smoking acts as a protective factor for UC.

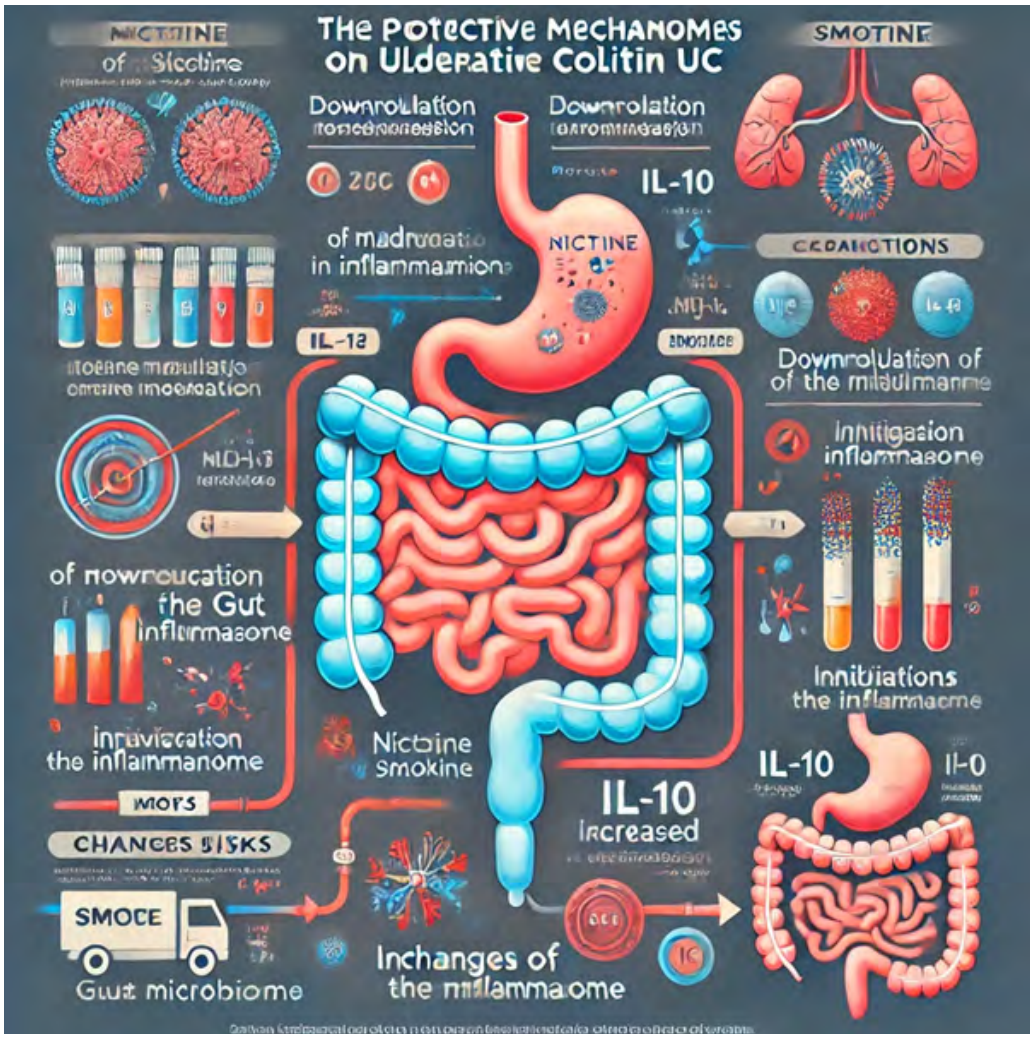

Figure 1: Summary of the main text information

3. Review Body

Epidemiological studies show that current smokers have a lower incidence of UC and tend to experience a milder disease compared to non-smokers and ex-smokers5,6. However, the precise mechanisms through which smoking exerts this influence remain a subject of ongoing study, and understanding these pathways is crucial for developing alternative, safer therapeutic strategies [5,6]. Nicotine, one of the primary active components of cigarette smoke, is thought to play a central role in smoking's protective effect5,6. Research indicates that nicotine can modulate immune responses and reduce inflammation in the colonic mucosa, a hallmark of UC pathology [5,6]. One way it achieves this is by downregulating the expression of mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is pivotal in leukocyte recruitment to inflamed tissues [7]. By limiting the infiltration of immune cells into the colon, nicotine helps mitigate the inflammatory response associated with UC [7]. Furthermore, nicotine has been found to inhibit the assembly of the NLRP3 inflammasome, a critical component of the innate immune system that drives inflammation in various diseases, including UC8. This inhibition may reduce the release of pro-inflammatory cytokines such as IL-1β and IL-18, both of which are implicated in UC pathogenesis [8]. Beyond nicotine, other components of smoke may also contribute to its anti-inflammatory effects by altering the gut microbiome [9]. Smoking has

been shown to influence gut microbial composition, potentially reducing the dysbiosis often observed in UC patients. Animal studies have suggested that cigarette smoke can restore microbial balance in the gut, which may help to resolve or prevent colonic inflammation9. These findings raise the intriguing possibility that microbiome modulation plays a role in smoking's protective effects, although more research is needed to fully elucidate these interactions [9]. In addition to microbiome alterations, smoking has been linked to the upregulation of anti-inflammatory cytokines, such as interleukin-10 (IL-10), in the colonic mucosa of UC patients [10]. IL-10 is a crucial regulator of immune tolerance and inflammation, and its increased expression in smokers may contribute to the attenuation of colitis symptoms by dampening the exaggerated immune response characteristic of UC10. This cytokine-driven anti-inflammatory effect could be another pathway through which smoking reduces disease activity in UC patients [10]. Despite these observations, it is important to stress that smoking carries substantial health risks, including an increased likelihood of developing cardiovascular disease, respiratory illnesses, and various cancers [7-9]. While the protective effects of smoking on UC have been documented, the overall detriments of smoking far exceed any potential benefits [7-9]. Smoking cessation should always be encouraged, and alternative therapies that mimic the anti-inflammatory effects of smoking, such as nicotine patches or other targeted immunomodulatory treatments, are being explored to offer safer options for managing UC7-9.

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