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Review Article

ROLE OF PLANT-BASED FLAVONOIDS AS DRUG CANDIDATES FOR INFLAMMATORY BOWEL DISEASE-A SHORT REVIEW

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ABSTRACT

Inflammatory Bowel Disease (IBD) is a chronic disorder caused due to several factors. Out of these, inflammation is one of the major causative factors, and several inflammatory markers, like pro-inflammatory cytokines enzymes play an essential role in the progression and development of IBD. The existing therapies against IBD have severe adverse effects, and drug resistance can also occur. Hence, novel therapies against IBD need to be developed for the treatment and prevention of IBD. Natural products, specifically flavonoids, can be an excellent alternative to get better therapeutic efficacy. Hence, flavonoids can be utilized more bitterly as a drug candidate for IBD. Our review work mainly discussed the potential flavonoids and their role in treating IBD and also focussed on it by inhibiting inflammatory markers.

Keywords: Plant-based flavonoids, Phytoconstituents, Drugs, Inflammatory bowel disease

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INTRODUCTION

Inflammatory Bowel Disease (IBD) is a complicated disease that is known for its prolonged conditions and occurrence throughout life. Nowadays, it is one of the major health concerns worldwide with less known pathophysiology and has become a burden for a larger population [1]. Usually, IBD is subdivided into two types: Ulcerative Colitis (UC) and Crohn's Disease (CD); in the case of CD, the inflammation affects any portion of the intestine but is usually detected at the colon and ileum. UC is a general chronic inflammatory condition of the colon and rectum that mainly affects the submucosa and large intestinal mucosa [2, 3]. Generally, IBD is treated by easily available marketed anti-inflammatory drugs and monoclonal antibodies targeting Tumor Necrosis Factor-α (TNF-α). Also, surgeries also used to be done to treat the same [4, 5]. Several research studies also suggested that a balanced diet can help to control and prevent IBD to a certain extent [6]. However, there are several disadvantages associated with existing therapies, as malignancy can happen due to TNF-α inhibitory agents, whereas intestinal perforation and hemorrhages can occur due to surgeries [7, 8]. So, nature-derived therapies can act as a potential alternative in this context and medicinal plants can be utilized as a lead for the same. Phenolics or polyphenolics are an important class of natural products which is generally identified by their aromatic or phenol ring structure. Further, they are classified into different sub-classes based on the phenolic rings present and the bonds that help to join those rings. Some important classes of phenolic compounds are flavonoids, lignans, stilbenes, hydroxycinnamic acids, etc., and usually, they act as anti-oxidant, anti-cancer, and anti-inflammatory agents [9, 10]. Phenolics, specifically flavonoids, are predominantly abundant in several dietary sources like carrots, strawberries, berries, grapes, apples, and tea [11, 12]. There are different experimental models of IBD are available, which are generally utilized to evaluate the inhibitory potential of medicinal plants, plant extracts, fractions, and isolated compounds against IBD [13]. Generally, inflammations are induced in rodent IBD models in different ways like immune cell transfer, chemical agents etc. Several chemical agents like 2, 4,6-Trinitrobenzene Sulphonic Acid (TNBS), Dextran Sulfate Sodium (DSS), etc. used to administer to express the inflammatory conditions [13]. Hence, this review summarizes the potential mechanism behind the inhibition potential of flavonoids against IBD, highlighting different experimental preclinical models (*in vitro* and *in vivo*) of IBD and it may also help researchers in their future studies in the same.

MATERIALS AND METHODS

The present review work has been done by thoroughly assessing research articles retrieved from different online databases like Wiley online library, PubMed, Springer link, Google Scholar, ScienceDirect, etc and in this work, different experimental animal models of IBD, evaluation of therapeutic potentials of flavonoids against IBD, clinical trials were covered. For this purpose, different keywords were utilized, like "Inflammatory bowel disease," "Pathophysiology of IBD," "Treatment for IBD," "Medicinal plants," "Phenolics, "Phenolics for IBD, "and "Animal models for IBD" etc.

Review

Role of flavonoids as therapeutic agents against IBD

Flavonoids, an important class of natural product, majorly isolated from medicinal plants, play an important role in the treatment of IBD. One of the key contributors to inflammatory bowel disease (IBD) is an imbalance in gut microbiota, which leads to excessive production of Reactive Oxygen Species (ROS) in intestinal epithelial cells. This ROS overload can damage tight junctions and increase intestinal epithelial permeability, ultimately compromising the intestinal barrier, triggering gastrointestinal inflammation, and contributing to the onset of IBD. Flavonoids, known for their potent antioxidant properties, help counteract these effects primarily by modulating the Nuclear Factor Erythroid 2–related factor 2 (Nrf2) signaling pathway, inhibiting Nuclear Factor Kappa B (NF-κB) activation, and regulating cell apoptosis [14, 15]. Several research works proved that different classes of flavonoids like flavones, is flavones, flavanols, flavanones, etc. showed moderate to significant inhibition against IBD in different experimental models. In this section, the protective role of different classes of plant-based flavonoids was discussed.

Flavonols

Quercetin

Quercetin (fig. 1.) is one of the most abundantly found flavonoids in nature and is present in numerous medicinal plants. It commonly

exists in its glycosylated forms like quercitrin and rutoside [16]. An experimental rat model developed by Comalada M *et al.* proved that quercetin offered excellent protection against DSS-induced colitis [17]. Some *in vitro* and *in vivo* studies successfully proved the inhibition potential of pro-inflammatory cytokines by quercetin [18]. Dodda *et al.* explained that quercetin rectifies colon damage, controls the regulation activities of MDA (Malondialdehyde) and MPO (Myeloperoxidase), and also the glutathione content was increased by it in a TNBS-induced mouse colitis model [19]. This phytoconstituent also treats DSS-induced colon injury in rats by downregulating the colonic NOS activity, and intestinal oxidative stress was also improvised by reducing the expression of iNOS (Inducible Nitric Oxide Synthase) protein [20]. Quercetin helps in the enhancement of particular protein expressions that are involved in the tight intestinal junctions, showing enhancement and reduction of intestinal integrity and intestinal permeability. It also protects the intestinal mucosal barrier [21-23].

Myricetin and kaempferol

Kaempferol (fig. 1) is an important flavonol class of phytocompound that helps in the effective treatment of inflammatory bowel disease. It was reported that kaempferol was successfully utilized as a supplement in a diet to mitigate DSS-induced colitis by decreasing several important inflammatory markers like iNOS, COX-2, IL-6 (Interleukin 6), TNF-α and it also helps to reduce the prostaglandin and nitric oxide levels in colonic mucosa [24].

Myricetin (fig. 1) is an important flavonol class of compound that is majorly isolated from the barks, leaves, and seeds of *Myrica rubra* [25, 26]. One research work stated that at the dose of 80 mg/kg this phytoconstituent effectively reduces ulcerative colitis and also plays an important role in the elevation of the levels of regulatory T cells [27].

Lcariin

Lcariin (fig. 1) is a flavonoid class of compounds (specifically 8-phenylflavonoid glycoside), and it is mainly isolated from the dried leaves and stems of *Epimedium koreanum, Epimedium pubescens,* etc. One research study showed that this phytocompound showed effective protection against DSS-induced enteritis in mice. While administered orally, Lcariin improves colitis-related pathological conditions and also disease progression will be postponed. It also decreases the pro-inflammatory mediators and isoforms of STAT enzymes in colonic tissues [28].

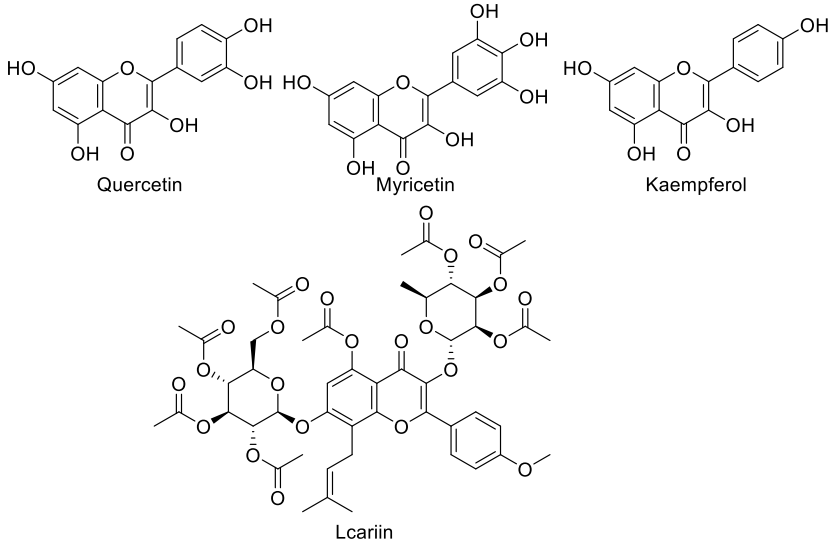

Fig. 1: Chemical structures of flavonols

Flavones

Apigenin

Apigenin (fig. 2) is a vital flavonoid that is majorly present in several fruits and vegetables, specifically in citrus fruits found in higher quantities [29, 30]. Several pieces of research demonstrated that apigenin can be useful for treating inflammatory bowel disease due to its anti-oxidant and anti-inflammatory activity. Out of these, one interesting study stated that apigenin offered excellent protection against colitis in DSS-induced mice. This effect may come due to the inhibition of several inflammatory markers like MMP-3 (Matrix Metalloproteinase 3), iNOS, IL-1b (Interleukin 1 Beta), COX-2 (Cyclooxygenase 2), and TNF-α [31].

Luteolin

Luteolin (fig. 2), also known as 3',4',5,7-tetrahydroxyflavone, is an important class of flavonoids that is majorly isolated from different plants like honeysuckle, garden bitter melon stems, celery, etc. [32, 33]. In several experimental models of IBD, it was observed that luteolin showed a potent protective effect. Out of these studies, an *in vivo* study done by Karrasch *et al.* stated that this phytoconstituent exhibited excellent protective action against colitis in IL-10 (Interleukin 10) deficient mice [34]. Nunes *et al.* proved that after treatment with luteolin, intracellular inflammatory signalling was modulated by the inhibition of the JAK/STAT pathway in HT-29 colonic epithelial cells [35].

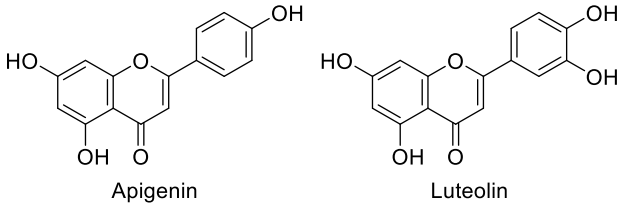

Fig. 2: Chemical structures of flavones

Flavanones

Naringenin

Naringenin (fig. 3), an aglycon part of naringin, is most commonly found in grapefruit and different research proved that it showed significant inhibition potential in different models of IBD [36-38]. A mouse model developed by Dou *et al.* exhibited that naringenin showed an excellent protective response against DSS-induced colitis. This protection may occurdue to the reduction of mRNA expressions of different factors responsible for inflammation like COX-2, IL-6, and TNF-α, etc [39]. It also reduced the expression of other inflammatory markers like Nitric Oxide (NO), prostaglandin, IL-1b, and IL-6 [40].

Farrerol

It is a 2, 3-dihydro flavonoid (fig. 3.) usually obtained from the Indian medicinal plant named rhododendron. One research study done by Ran *et al.* demonstrated that this phytoconstituent showed a significant reduction in several important inflammatory mediators like Il-1β, TNF-α, and IL-6 in RAW 264.7 cells [41]. It also can offer protection against TNBS-induced colitis in a mouse model [42].

Hesperetin

Hesperetin (fig. 3.) is an important flavanone glycoside, also known as 5,7,3'-trihydroxy-4'-methoxy flavanone is most commonly found in citrus fruits like oranges, limes, mandarins and lemons, etc. [43-45]. At the doses of 50 and 100 mg/kg, hesperetin showed significant improvement in the TNBS-induced colitis symptoms in the experimental rat models like recovering from macroscopic colon damage [46]. One more piece of research work proved that this phytoconstituent can successfully alleviate colitis by blockade of the intestinal epithelial necroptosis in the DSS-induced experimental mice model [47]. Hesperetin (at the dose of 100 mg/kg) also offered excellent protection against TNBS-induced colitis in the respective rat model [48].

Anthocyanin

Anthocyanin (fig. 3.) is a water-soluble flavonoid and is mainly obtained from fruits like red grapes, Murray, purple cabbage, blueberries, blackberries, etc. Basically, it is a coloured aglycone formed after hydrolyzing anthocyanins [49-51]. Wu *et al.* developed a TNBS-induced experimental mice modeland reported that at the doses of 40, 20, and 10 mg/kg, blueberry-derived anthocyanins exhibited a significant role in the same [52]. It was also observed that the anthocyanins extracted from bilberries and black rice showed potent efficacy in the relief of colitis [53, 54].

Isoflavones

Genistein

Genistein (fig. 4) is an important class of isoflavone, which is also known as 4′, 5, 7-trihydroxy isoflavone is commonly obtained from soy milk, soy cheese, etc. [49, 50]. Zhang *et al.* observed that at the dose of 600 mg/kg, genistein reduced gut dysfunction and colonic inflammatory conditions in the DSS-induced colitis BALB/C mice model [55]. Abron *et al.* proved that at the dose of 10 mg/kg, this phytoconstituent effectively reduced the progression of ulcerative colitis in a DSS-induced experimental mice model [56].

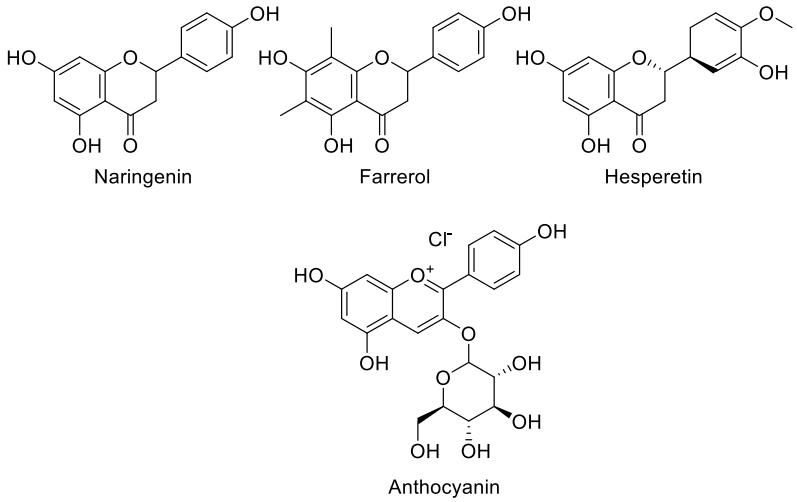

Fig. 3: Chemical structures of flavanones

Catechins

Catechins (fig. 4.) generally contain the parent structure of flavonoids and are mainly found in medicinal plants like grapes, apples, legumes, buckwheat, tea, etc. [57-59] and generally classified into different types, such as epicatechin, epicatechin gallate, (2)-epigallocatechin-3-gallate, etc. Du *et al.* 2019 observed that at the dose of 20 mg/kg, epigallocatechin exhibited better efficacy in the DSS-induced colitis model [60]. It also helps to mitigate the DSS-induced colitis (at the dose of 50 mg/kg) in the experimental rat model by showing potent inhibition of inflammatory markers [61, 62].

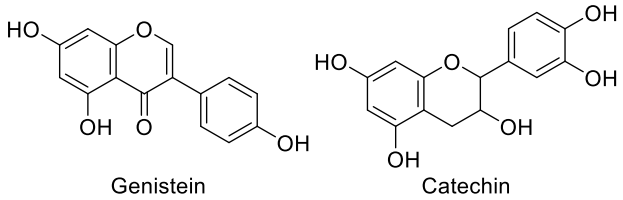

Fig. 4: Chemical structures of isoflavones

Through this discussion, it became evident that flavonoids can be further utilized for the development of novel therapies against IBD. However, flavonoid-based drug development often faces challenges related to low bioavailability, poor absorption, and other issues. To overcome these challenges, researchers suggested several techniques so that more efficient therapies can be developed. Absorption efficiency is influenced by glycosylation; for instance, quercetin in its glycosylated form is more readily absorbed, whereas catechin, a non-glycosylated flavonoid, is absorbed with comparable efficiency. For example, the reduced absorption of certain flavonoids, leading to higher colonic concentrations, suggests their potential role in mitigating inflammatory bowel disease (IBD) pathogenesis [63]. To increase the bioavailability of flavonoids *in vivo*, scientists focus on improving some metabolic processes related to bioavailability, such as boosting intestinal absorption, improving metabolic stability, moving absorption site, and so on. Nano-delivery techniques have been used to achieve the aforementioned goals with flavonoids. Recently, with the discovery of biodegradable polymers, flavonoid-loaded polymeric NPs have become an increasingly popular therapeutic approach for IBD, as they can increase stability and absorption while also changing the absorption site [64]. While flavonoids have health advantages, many data have also confirmed that flavonoids have exhibited significant liver-protection and renal-protection properties *in vitro* and *in vivo* [65]. Few studies have even highlighted the toxicity issues related to the usage of flavonoids. One such study stated that large doses of epigallocatechin gallate (EGCG) may cause hepatotoxicity and nephrotoxicity. The specific causes are unknown, although it is suggested that high ingestion may cause oxidative stress, which contributes to liver and kidney damage. Similarly, quercetin has been associated with kidney damage. Flavonoids may also have an effect on thyroid function, with the effects varying depending on the duration of consumption and exposure. Although multiple *in vitro* and *in vivo* studies indicate that flavonoids can interfere with thyroid metabolism, the underlying mechanisms are complex and warrant additional exploration. Notably, quercetin has been reported to have thyroid-disrupting effects [66].

CONCLUSION

Inflammatory bowel disease is one of the most prevalent diseases spreading all over the world, and novel therapies need to be developed to treat it. Natural products, specifically plant-based, play an important role in the same and can be utilized for developing safer and more efficacious treatments against IBD. In our current review work, the role of plant-based flavonoids in the treatment of IBD was explained by demonstrating the published scientific works that showed this class of phytocompound showed moderate to good results in different *in vitro* and *in vivo* models. Our work also described that inflammation exerts a key role in the progression of IBD, and the same can be inhibited by decreasing or downregulating different inflammatory markers like IL-1b, IL-6, TNF-α, etc. Also, information related to some experimental animal models was discussed which may help the researchers to do future work in this direction. However, further clinical studies need to be done in order to get more information regarding the safety, clinical efficacy, and dosage of the natural flavonoid compounds so it helps for further drug development.

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AUTHORS CONTRIBUTIONS

Samriti Faujdar: Resources, Supervision, Validation, Visualization, Writing – review andamp; editing

Prabha Hullatti: Conceptualization, Data curation, Formal analysis, Software, Methodology, validation, Visualization, Writing – original draft.

Nabarun Mukhopadhyay: Conceptualization, Data curation, Formal analysis, Software, Methodology, validation, Visualization, Writing–original draft.

A P Basavarajappa: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Visualization, Writing–original draft.

Saraswati Patel: Conceptualization, Data curation, Formal analysis, Software, Methodology, validation, Visualization, Writing – original draft.

CONFLICT OF INTERESTS

Declared none

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