Chapter

Review and Implications of Traditional Indian Medicine for Inflammatory Bowel Disease

Uma Ranjan Lal and Inder Pal Singh

Abstract

Inflammatory bowel disease (IBD) is a group of intestinal disorders that cause prolonged inflammation of digestive tract. Chronic inflammation results in Crohn's disease (CD) and ulcerative colitis (UC). There is a disruption of homeostasis of various regulatory factors, for example, cohesive functioning of intestinal epithelial barrier, macrophages, and cellular mediators such as cytokines and chemokines. Natural products derived from plants based on traditional system of medicine have exhibited efficacy for UC and CD in experimental models and clinical trials. In the present review, current developments of natural products and herbs for the treatment of IBD in the context of Indian traditional medicine have been highlighted. Two classes of Ayurvedic formulation, fermented preparations (*Asava* and *Arishta*) and *Ghrita* (preparations involving butter), are employed for the maintenance of intestinal disorders. Here, we discuss mainly about the fermented preparations, their main constituents, and correlations with modern findings. The way these fermented formulations are processed also affects the extraction of constituents in them. So, the correlation between the chemistry of the plant material (their constituents as well) with the IBD was done. These correlations may serve as a step forward to reduce the gap between modern system of medicine and traditional system of medicine.

Keywords: inflammatory bowel disease, traditional system of medicine, fermented preparations, gallotannins, ellagitannins

1. Introduction

Inflammatory bowel disease (IBD) is the intestinal disorder induced by chronic gastrointestinal inflammation. Crohn's disease (CD) and ulcerative colitis (UC) are global health problems, with the highest incidence and a prevalence rate of 0.5–1.0% in Europe [1]. The incidence of IBD is increasing dramatically in Asian countries, especially in China. There is rising incidence and prevalence of inflammatory bowel disease in India, topping the Southeast Asian (SEA) countries [2]. IBD is relatively complex disease that involves numerous factors such as commensal flora, genetic factors, immune system dysfunction, and environmental risk factors [3]. The human gastrointestinal tract serves as the first-line sensor, and defense against external environment stimuli is exposed to the external environment, particularly to bacterial antigens released from resident microbiota. It is the chronic inflammation in the intestinal surface that first leads to the development of UC,

which can progress into CD and/or colon cancer [3]. Advances have been achieved in understanding the pathogenesis of IBD in the past few years, yet exact mechanisms remain to be elucidated. Patients usually suffer from severe pain, diarrhea, abscesses, fistulas, abdominal pain, and stenosis. Thus the development of effective treatments and/or reducing the symptoms of patients with IBD is urgently needed. The current mainstream management of IBD includes antibiotics, corticosteroids, thiopurines, anti-tumor necrosis factor (TNF) antibodies, and aminosalicylates [2]. They have severe side effects such as diarrhea, nausea, vomiting, headache, and osteoporosis when used for the long term. One-third of CD patients undergo surgery after long-term use of these mainstream treatments [4].

The Indian System of Medicine which mainly comprises of Ayurveda (meaning the *science of life*) is one of the oldest systems of medicine in India. This system of using natural resources for better health was developed through the experimentation and experiences of day-to-day lifestyle of Indian people. Evolution of Ayurveda and plant-based remedies for health care through day-to-day life experiences is a part of cultural heritage of India. There is class of Ayurveda fermented preparations called *Asava* and *Arishta* mainly intended for intestinal disorders. These weak alcoholic preparations are more appreciated because of their quick action and high preserving qualities. These preparations are made by soaking the drugs, either powder form or in the form of decoction in a solution of sugar or *jaggery*, as the case may be for a specified period of time, during which it undergoes fermentation. It facilitates dissolution of active principles and acts as a preservative. For *Arishta* preparation, the drugs mentioned in the text are coarsely powdered, and the decoction is prepared by boiling the plant material in a specified volume of water till it is reduced to one-fourth of the original volume. The decoction is filtered using muslin cloth. *Jaggery* as prescribed in formula is added and dissolved. Drugs indicated as *prakshepa dravyas* (plant material added after preparing decoction) are finely powdered and added. At the end *Woodfordia fruticosa* (*Dhataki pushpa*) if mentioned is added. The container is then sealed and kept for fermentation and monitored regularly. After the fermentation is over, the fluid is decanted without disturbing the sediment. The decanted preparation is then kept for maturation for 2 weeks. The fine particles in the decanted preparation settle down (**Figure 1**) [5, 6].

The present review mainly discusses the fermented preparations used in *Ayurveda* for the intestinal disorders and correlates the constituents used for the same. For the preparation of formulations in ancient times, mainly decoctions were used, and then they were preserved by some processing methods, as fermentation in the case of *Asava* and *Arishta*. During the making of formulations, it is the water-soluble ingredients that are mainly extracted to water, and during fermentation they are transformed fit for the body to be absorbed and are medicinally active. The formulations (*Parthadyarishta, Abhayarishta*, *and Jirakadyarishta*) have shown certain chemical changes during fermentation due to which the desired marker constituents in the decoction are transformed: polyphenolics to their monomeric counterparts and glycosides to their respective aglycones [7–9]. HPLC analysis of the selected formulations revealed that it is the polyphenolics which are easily decocted into water and they form the major constituent of these liquid oral formulations. There is also a breakdown of high molecular weight polyphenolics into the low molecular weight phenolics as evident from the quantitative analysis of the formulations. The changes in marker concentrations during fermentation also affect the antioxidant activity of the decoction and formulation [7–9]. Major constituents in these formulations based on their analysis have revealed the presence of polyphenolics (gallotannins and ellagitannins), flavonoids, 5- HMF, and phenolic glycosides, and constituents of jaggery formed the major constituents in the formulation. These constituents are correlated with modern finding in next section.

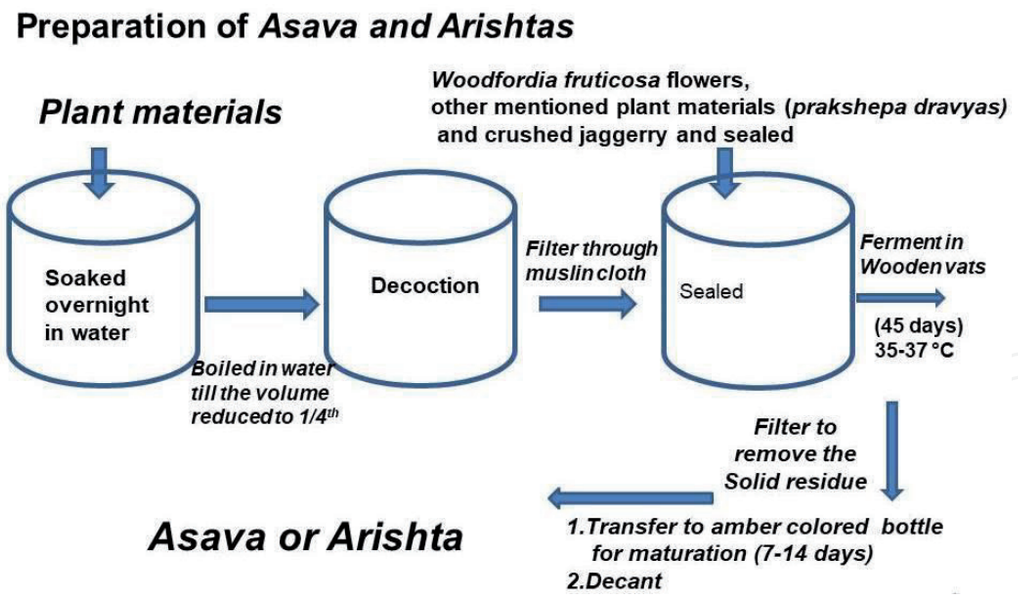

Figure 1.
Method of preparation of fermented preparations in Ayurveda.

2. Major constituents present in fermented preparations and correlation with inflammatory bowel disease

2.1 Gallotannins

Gallotannins are a major constituent of plant materials used for the preparation of fermented preparation *Abhayarishta*. The pericarp of *Terminalia chebula* fruit is used in the preparation which is rich in hydrolyzable tannins and is reported to contain the following constituents: chebulic acid (**1**), gallic acid (**2**), ethyl gallate (**3**), polygalloyl derivatives (**4–6**), chebulinic acid (**7**), chebulanin (**7a**), chebulagic acid (**8**), terchebin (**9**), and terchebulin (**10**). During the making of formulation, pericarp powder is boiled in water till the volume is reduced to one- fourth, and this process mainly decocts the hydrolyzable tannins. During fermentation these gallotannins are fermented to their monogalloyl and digalloyl derivatives (**5**) and other counterparts (chebulic acid (**1**) in case of *T. chebula*). The fermented counterparts in case of their preparations have shown more antioxidant activity [7]. They may have very good effect on IBD also as have shown to good inflammatory agents. For example, chebulic acid (**1**) inhibits TNF-α, TNF-α, IL-1β, and IL-6 as well as enhances antioxidant detoxification defensing mediators such as HO-1 and NQO1 expression, through ERK/Nrf2 signaling in HUVEC [10, 11]. It may be noted that tannins in case of *T. chebula* are of chebuloyl derivative [12], and during fermentation **7**, **7a**, and **8** will be hydrolyzed in acidic conditions to chebulic acid (**1**). It is also one of the major constituents in the formulation *Abhayarishta* [7]. Other constituents formed in final processed formulation during fermentation were monogalloyl derivatives and digalloyl derivative. This could be attributed to the presence of free galloyl group at anomeric carbon that makes chebulinic acid (**7**) and chebulagic acid (**8**) susceptible for cleavage [13]. Moreover, the amount of chebulinic acid (**7**) in decoction was found to be less (which is normally 2–4% of total dry weight of plant material). The reason for this may be the possible hydrolysis of the chebulinic acid (**7**) during boiling (as simple boiling resulted in hydrolysis) or less extraction of the same due to its hydrophobic properties resulting from free galloyl groups [13]. Ethyl gallate (**3**) and gallic acid (**1**) were formed as hydrolytic products and ethanolysis of tannic acid (**Figures 2** and **3**). These fermentation products had better

radical scavenging activity [7], and among them gallic acid (**1**) has shown to induce ROS-dependent apoptosis and inhibited the growth of colon cancer cells [14]. These formulations are used as nutraceuticals in the Indian subcontinent [15], and the constituents present in the formulation (or formed during the fermentation) have good anti-inflammatory properties as discussed above.

2.2 Ellagitannins

Ellagitannins are the other major phytoconstituents that are extracted during the boiling/maceration with water. This is mainly due to the presence of hexahydroxydiphenic (HHDP) moiety in ellagitannins [13]. Their extractability in water is more than the gallotannins. Terchebulin (**9**), punicalagin (**10**), and punicalin (**11**) are the major ellagitannins present in decoction and are fermented to increase concentration of ellagic acid in the final formulation [7, 12]. Studies have shown that there is formation

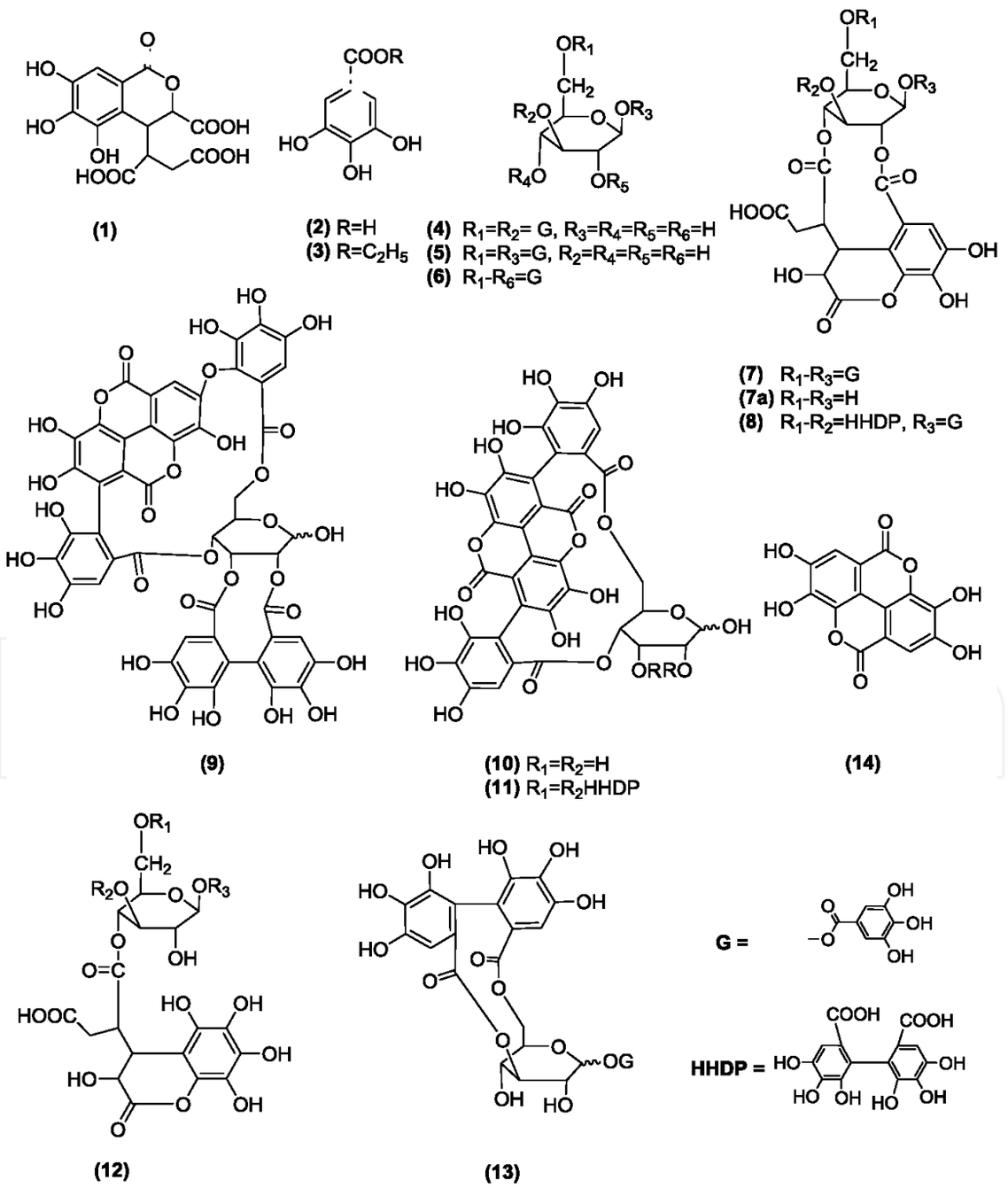

Figure 2.
Structures of compound present in T. chebula *(**1–14**).*

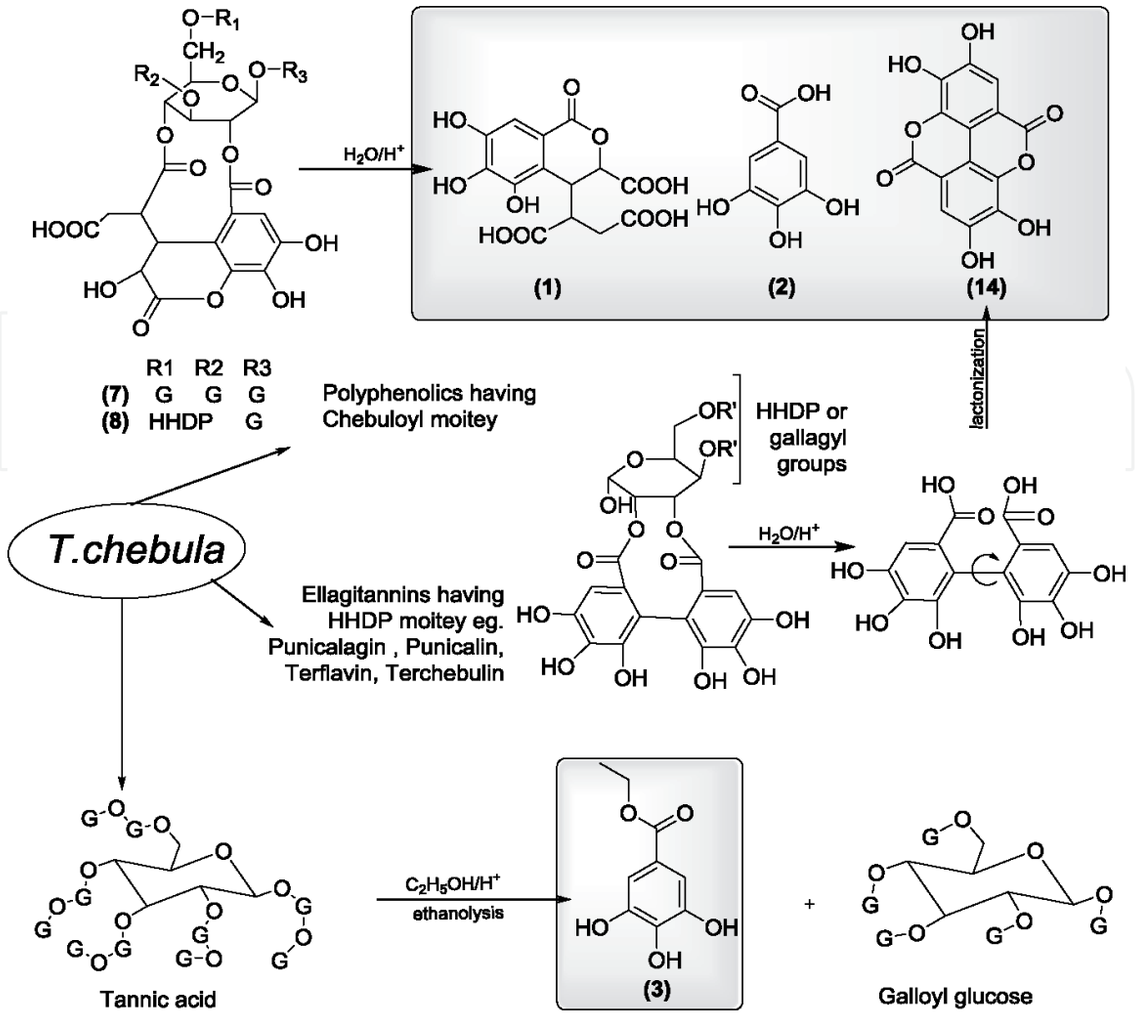

Figure 3.
Possible changes during fermentation in Abhayarishta.

of urolithin A, B, and C by human gut microbiota when an ellagitannin-rich diet was given, and also these urolithins significantly inhibited TNF-α production. The most potent urolithin A inhibition was observed at nanomolar concentrations (at 0.625 μM 29.2 ± 6.4% of inhibition). Urolithin C was the only compound inhibiting IL-6 production (at 0.625 μM 13.9 ± 2.2% of inhibition) [16]. These studies clearly indicate that ellagitannin-rich plant material extract has a good effect on gut microbiota. A combination of the ellagitannin metabolites found in the colon, urolithins and ellagic acid, at concentrations achievable in the intestine after the consumption of pomegranate, was able to moderately improve the inflammatory response of colon fibroblasts and suggest that consumption of ellagitannin-containing foods has potential beneficial effects on gut inflammatory diseases [17]. Effectiveness of polyphenols in dysbiosis and colon-related diseases mainly depends on their stability, absorption, and bioavailability and the gut microbiota composition [18]. Encapsulation technologies could be promising tools to improve bioavailability and bio-accessibility of polyphenols. In recent studies, several micro- and nano-encapsulation systems have been proposed for specific delivery of individual polyphenols or mixtures of polyphenols (food ingredients) in the gut [19].

2.3 Flavonoid glycosides and aglycones

Flavonoid glycosides and phenolic glycosides are the other class of phytoconstituents that are extracted in substantial amount during the boiling of plants during preparation of formulation. These were evident when formulations like

Jirakadyarishta and *Parthadyarishta* were analyzed for standardization purpose [8, 9]. The chemical constituents that are present in cumin seeds (major plant material in *Jirakadyarista*) are water-soluble flavonoid glycosides luteolin 4′-O-glucoside 7-O-galacturonoside (**15**), apigenin-7′-digalactouronoside (**16**), luteolin 7-O-glucoside (**17**), apigenin 7-O-glucoside (**18**), flavonoid aglycones luteolin (**19**), apigenin (**20**), sesquiterpene lactone glucosides, cuminoside A (**21**) and cuminoside B (**22**), cumic acid (**23**), cuminyl alcohol (**24**), glycosides of 2-C-methyl-D erythritol, alkyl glucosides, and various monoterpene glycosides [20–25].

RP-HPLC analysis of the decoction and the final processed formulation revealed that luteolin 4′-*O*-glucoside 7-*O*-galactouronoside (**15**) and luteolin 4′-O-glucoside 7-O-galactouronoside (**16a**) were the two major constituents of the decoction of *C. cyminum*. Selective hydrolysis of 7-O-glucosides of luteolin and apigenin during fermentation resulted in an increase in the amount of luteolin and apigenin in the final processed formulation. The 4′-O-glucoside-7-O-galacturonide of luteolin and galacturonide derivative of apigenin was not hydrolyzed during fermentation [9]. An increase in luteolin and apigenin concentration is also good for the gut health as recent studies have shown that flavonoids participate in the regulation of intestinal tight junction barrier integrity and that this regulation may partially contribute to the flavonoid-mediated biological effects on our health [26]. Dietary flavonoids are often transformed before absorption, and this transformation modulates their biological activity. Health benefits from this aglycone consumption should be attributed to their bioactive metabolites and also to the modulation of the intestinal bacterial population [27]. Flavonoids are the major constituents in the formulation, and various beneficial actions of flavonoids at the GI have been demonstrated through various reports, for example, (i) protection of the intestinal epithelium against pharmacological insults and food toxins and (ii) modulation of the activity of enzymes involved in lipid and carbohydrate absorption. Thus, they maintain the intestinal barrier integrity and modulate the secretion of gut hormones and finally modulate the GI tract immune system. They also have been shown to exert potential anti-colorectal cancer activity by shaping microbiota composition and function. The understanding of the mechanisms mediating the effects of flavonoids on the intestine (and its microbiota) is further required for the widespread recommendations of increasing the intake of plant bioactives [28].

Further, the addition of *Woodfordia fruticosa* for augmenting fermentation also adds flavonoid glycosides to the formulation in major quantity, as evident in the studies done on *Parthadyarishta,* where flavonoid aglycones quercetin and kaempferol were produced as fermentation products from flavonoid glycosides of *Woodfordia fruticosa* [8]. Thus these flavonoid glycosides and aglycones are present in substantial quantity in these formulations and have well-reported protective actions against the IBD through various mechanisms.

2.4 5-Hydroxymethyl furfuraldehyde (5-HMF)

5-Hydroxymethyl furfuraldehyde, 5-HMF (**25**), is another major constituent which is ought to be present in this class of formulation as per the analysis done for the selected formulations. 5-HMF is also present in decoction of fruits and flowers (*V. vinifera and M. indica*) used for preparation of fermented preparations. Another source for **25** in final processed formulation is jaggery and honey which is added in a substantial amount to augment fermentation (**Figures 1** and **4**). 5 -HMF is the major compound extracted during boiling and forms the major constituent in the formulation and is also reportedly formed under acidic conditions from fructose [29]. There was an enormous increase in amount of 5-HMF (**25**) in formulation as compared with decoction. The concentration of **25** needs proper monitoring in this class of formulations as recent reports suggest it to be genotoxic and cytotoxic [30].

Further, Maillard reaction product components, namely, 5-hydroxymethyl furfural and 5-hydroxymethyl-2-furoic acid (HMFA), were shown to have bioactive potential, especially in regard to suppressing oxidative stress and inflammation in IFN-γ- and PMA-induced Caco-2 cells [31]. 5-Hydroxymethyl furfural (HMF)–cysteine adduct, 1-dicysteinethioacetal–5-hydroxymethyl furfural (DCH), promoted the growth of *Lactobacillus*, *Tyzzerella*, *Enterobacter*, and *Streptococcus* and also increased

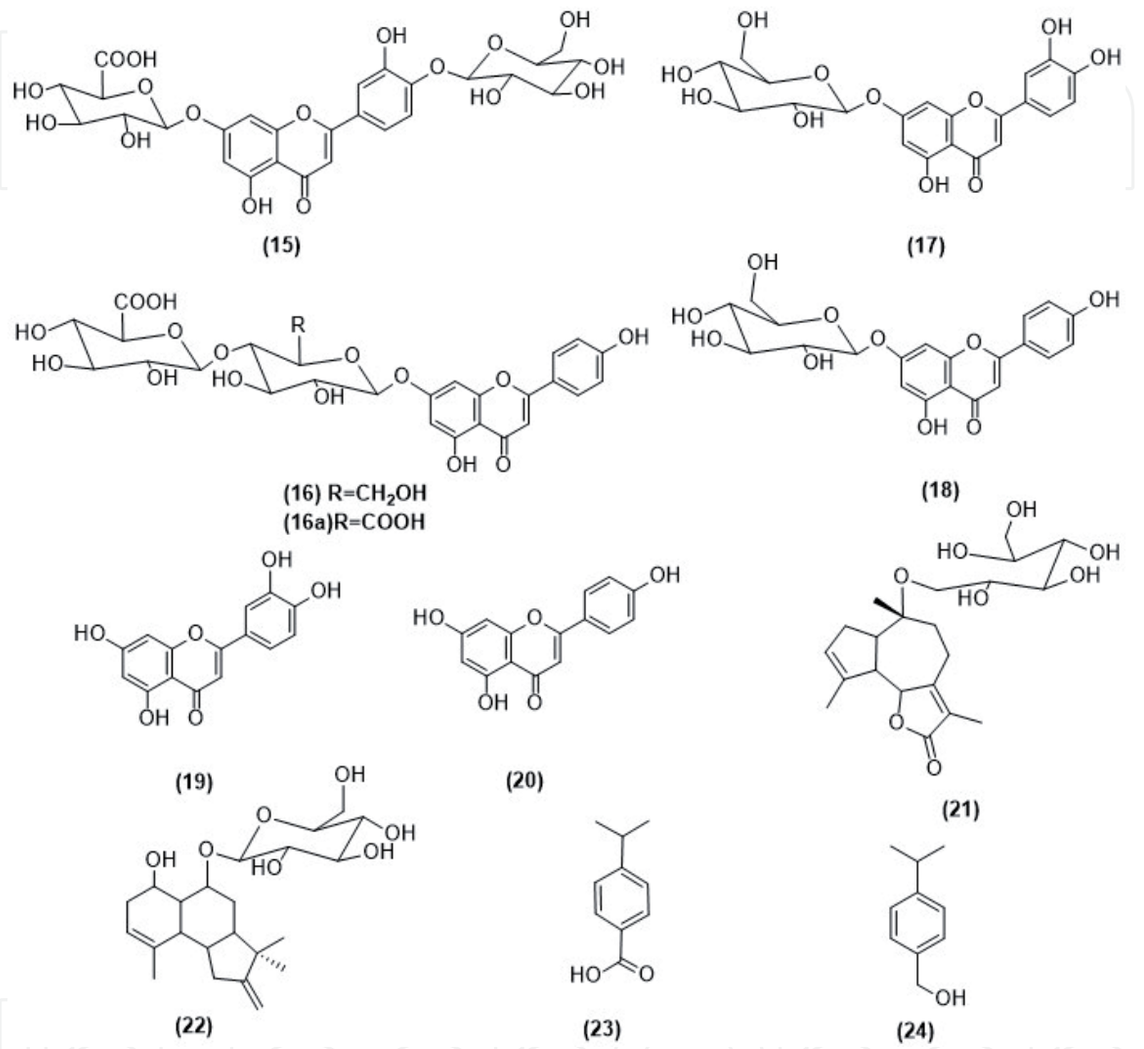

Figure 4.
Water-soluble constituents in cumin Cuminum cyminum *seeds.*

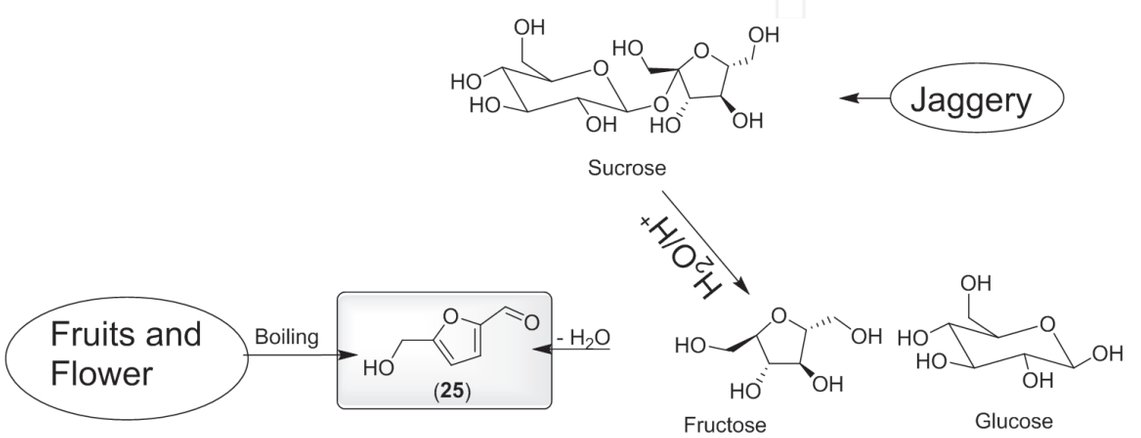

Figure 5.
*5-HMF(**25**) as major constituent in fermented preparation.*

the ratio of *Firmicutes*/*Bacteroidetes* and promoted the growth of *Akkermansia*, *Shigella*, and *Escherichia* while inhibiting the growth of *Lactobacillus* [32]. Thus these reports are suggestive of their usage in controlling IBD (**Figure 5**).

2.5 Bioactives present in jaggery

Jaggery constitutes a major part in this class of formulation. It is also used very frequently in other class of Ayurvedic formulations. Jaggery is traditionally made

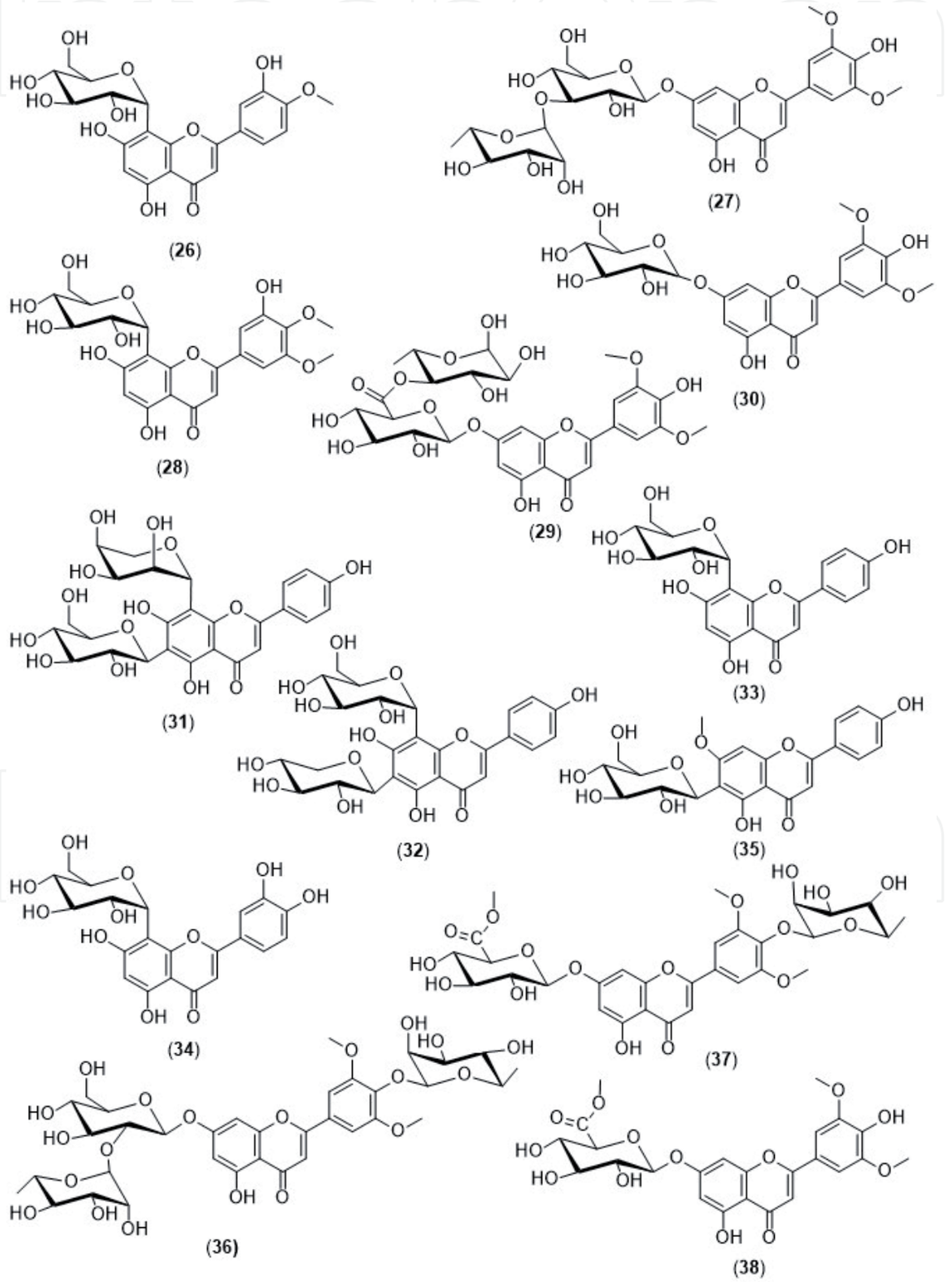

Figure 6.
Flavonoid glycosides in sugarcane juice: (27–38).

by boiling sugarcane juice to solid [33]. A review of chemistry of sugarcane juice and its products reveals that they are rich in phenolics, phenolic glycosides, and flavonoid glycosides (**Figure 6**), namely, diosmetin-8-*C*-glucoside **(26)**, tricin-7-*O*-neohesperidoside **(27)**, 4′,5′-dimethoxy-luteoline-8-*C*-glucoside **(28)**, tricin-7-*O*-rhamnosylgalacturonide **(29)**, tricin-7-*O*-glucoside **(30)**, schaftoside **(31)**, isoschaftoside **(32)**, vitexin **(33),** and orientin **(34)**. Four minor flavones swertisin **(35)**, tricin-7-*O*-neohesperoside-4'-*O*-rhamnoside **(36)**, tricin-7-*O*-methylglucuronate-4'-*O*-rhamnoside **(37),** and tricin-7-*O*-methylglucuronide **(38)** were isolated and identified from sugarcane juice [34–39]. There are health benefits from phenolic consumption, mainly attributed to their bioactive metabolites and also to the modulation of the intestinal bacterial population. Phenolic contents of the herbal preparation can be increased as a consequence of fermentation, and a positive correlation between polyphenols and the antioxidant activities of herbs has been well demonstrated. This is in agreement with evidence showing fermentation-mediated enhancement of the pharmacological properties and therapeutic efficacies of herbal formulations against a number of diseases including obesity and inflammation [27].

3. Conclusions

From the evidences cited above, it is very clear that herbal formulations and their analysis for the presence of bioactive constituents are important as far as their efficacy is concerned. Three formulations have been cited, and major constituents present in them have proven to be good agents for IBD. Natural products and herbal medicine formulas have exhibited efficacy in preclinical evaluation, improved symptoms, and decreased medical costs for IBD patients. The components of natural products and herbs are complex and have multiple mechanisms of action that may synergize to produce their overall efficacy. Intensive studies based on murine models of IBD and human studies are required for evaluating the efficacy of natural products and herbal medicine as an alternative treatment for IBD. Thus identification of the active component(s) and optimization of the dosage and development of treatment protocol(s) are of primary importance. The modern hyphenated techniques having high-throughput technologies shall enable the identification of the effective ingredient(s) and reveal the mechanisms of action of natural products and herbs in treating IBD. Natural products and herbal formulations (as co-adjuvants) with existing medications may also provide new therapy options for IBD patients.

Conflict of interest

Authors declare no conflict of interest.

Author details

Uma Ranjan Lal[1*] and Inder Pal Singh[2]

1 Department of Natural Products, National Institute of Pharmaceutical Education and Research, Ahmedabad, Palaj, Gandhinagar, Gujarat, India

2 Department of Natural Products, National Institute of Pharmaceutical Education and Research, Mohali, Punjab, India

*Address all correspondence to: urlalvv@yahoo.com

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