

# Herbal remedies are the main etiologic factor in melanosis coli, a case series study

Research Article

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**Abstract:** Melanosis coli is a brown to black discoloration of the colon mucosa usually associated with long-term ingestion of laxatives. However, melanosis coli can be found in patients with no history of laxative use. Regular use of herbal remedies could be the major source of anthranoid laxatives in such patients. We designed a prospective case series study to identify the clinical characteristics and etiology of melanosis coli in affected patients. This study took place in Ankara, Turkey, between 08/2005 and 11/2006. Patients with endoscopic diagnosis of melanosis coli were interviewed for demographical data and use of herbal remedies. A total of 380 colonoscopies were performed during this period. Melanosis coli was diagnosed endoscopically in 12 patients (3.17%), 11 of whom were found to have characteristic pigment-laden macrophages in histopathological examination. Herbal remedies were the main etiological factor in the development of melanosis coli in 10 out of 11 patients. Diffuse involvement was found in 2 patients who had a history of long-term use. In 8 patients, melanosis coli was located in the left side of the colon. Although melanosis coli is a harmless discoloration of colonic mucosa resulting from complementary or alternative medicine, we believe that this association with herbals was overlooked or not inquired in patients. Therefore, it should be emphasized that “natural” or “alternative” is not equal to “safe”.

**Keywords:** *Melanosis coli* • *Herbal remedies* • *Laxatives* • *Sennosides* • *Etiology*

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## 1. Introduction

Colonoscopy has increasingly been used in the investigation of patients with lower gastrointestinal (GI) system symptoms like chronic constipation and diarrhea. This procedure has the advantage of obtaining biopsies for pathologic study for confirming diagnoses. Routine colonoscopy examinations may sometimes reveal Melanosis Coli (MC). MC is a well-known condition that is associated with long-term use of anthranoid-containing laxatives [1]. MC refers to brown-to-black pigmentation of colonic mucosa that can occur within several months of regular use and can last for nearly one year after discontinuation of the laxative use. This pigment is related to lipofuscin, a wear-and-tear product, which is released during cellular apoptosis and is contained in mucosal macrophages [2,3].

Because of the well-known association with anthranoid laxatives, almost all MC patients are asked about laxative abuse. MC has also been found in patients who have no history of laxative use.

The use of complementary and alternative medicine (CAM) by the general public is prevalent, and the number of patients looking for nonconventional practices to manage their chronic diseases is increasing. Among the U.S. general population, for instance, the 1-year prevalence of CAM use rose from 33% in 1990 to 42% in 1997. Therefore, it is not surprising to encounter dissatisfied patients, for whom conventional therapies have failed, searching for other possibilities [4-7].

It has been estimated that 28.9% of U.S. adults use CAM in some form. Herbal medicine is one of the most common CAM modalities. It has been estimated that between 9.6% and 12.1% of U.S. adults use some form of herbal product [5].

Herbal remedies are mostly used for gastrointestinal diseases, and these preparations often contain laxatives. There is a trend towards using a mixture of herbal teas to lose weight. A study from Turkey has found that all of the 13 commercial and handmade mixtures of diet-form teas sold by herbalists contain senna in significant amounts [8]. A couple of cups of tea can contain a

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therapeutic dose of laxatives. As most patients do not inform their doctors about taking CAM, it is not surprising that information about MC is overlooked. Some of the patients with MC report that they do not take laxatives; however, in the case of herbal therapy, its role in this group of patients is unclear. A study from Korea aimed to determine the relation between colonic transit time and constipation and to identify the clinical characteristics of patients with MC. This study reveals anthranoid laxatives as a major cause; however, teas, herbs, and health foods comprise 30% of the cases as a cause. There is no information about the type of herbs. This study reports herbal remedies as a cause of MC along with laxatives [9]. It is clear that senna-containing teas or herbals could lead to MC. To date, there is no study investigating MC and the use of anthranoid-containing herbal remedies without a history of laxative drug use. We aimed to report our experience with MC and to compare the results with published data with special emphasis on herbal medicine as the primary offending agent.

## 2. Material and Methods

This is a case series study to identify the clinical characteristics and etiology of MC in affected patients.

Between 2005 and 2006, all consecutive patients who underwent total colonoscopy at the endoscopic unit of 29 Mayıs Hospital were considered for evaluation. This is a private hospital in Ankara serving the general population as a secondary-care center. The gastroenterology practice is busy, with the ability to perform most of the diagnostic and therapeutic interventions. Pathological examinations are outsourced to a private out-of-hospital pathology center. The endoscopy center has been working as an open-access center responding to requests from other departments in the hospital. After the index case of MC with consumption of herbal teas containing senna, we decided to search the role of herbal teas, remedies or medicines in the development of MC. We included patients with an endoscopic diagnosis of MC. We had a total of 380 colonoscopies performed during the stated period. We excluded left-sided colonoscopies and sigmoidoscopies, although we did not in fact have any patient diagnosed with MC during these procedures.

The same endoscopist (T.K.) did all the colonoscopies. The examinations reached as far as the terminal ileum in most of the cases. Mucosal changes were noted for the distribution, severity and form of the pigmentation.

Endoscopic diagnostic criteria for MC were dark pigmentation of the mucosa from light brown to black, sometimes with a leopard-skin or reticulated pattern, and dilated colon segments with loss of haustra. As MC usually affects the proximal colonic segments first, special care was given to any discoloration of the proximal colon; even hardly visible brown speckles were biopsied. All of the patients included in this study had the signs of MC at colonoscopy.

MC diagnoses were confirmed by pathological examination. Paraffin sections obtained from the caecum and ascending colon were stained with haematoxylin and eosin (H&E). Patients with characteristic pigment-laden macrophages found in the lamina propria are considered to have MC.

After the colonoscopic diagnosis of MC, patients were interviewed by an investigator. Patients were investigated for the long-term use of laxatives, presence of constipation or diarrhea, and other clinical findings. Patients with MC were also asked for the use and length of use of any type of complementary and alternative medicine practices, especially herbal remedies for various reasons. We received information on usage, duration, and type of CAM. Patients were asked for any benefit from CAM. Patients were also asked for knowledge about CAM practices such as side effects and any side-effect experience. Finally, we asked if they had provided information to their physician about using herbal remedies regularly before any decision was made to schedule an examination.

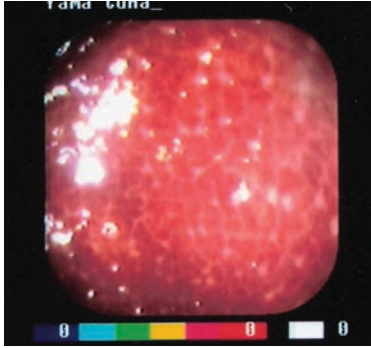
## 3. Results

A total of 380 colonoscopies were performed between 2005 and 2006. Successful colonoscopy was achieved in 346 patients, thereby reflecting a success rate of 90%. Reasons for unsuccessful colonoscopies were inadequate bowel cleansing in 22 patients, the patient's nontolerance and pain in 4 cases, and technical difficulty due to redundant bowel segments in 8 patients.

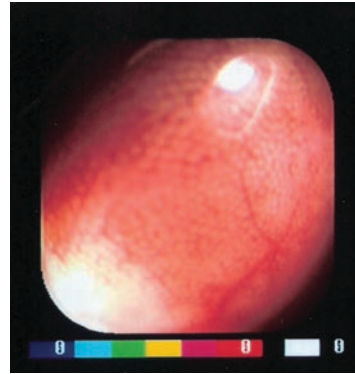
During this period, 12 patients were endoscopically diagnosed as having MC. MC incidence among patients who underwent colonoscopy was 3.16%. Most of the patients were female; the female-to-male ratio was 10/2. The patient mean age at the time of diagnosis was 53.9 years (min: 46; max: 79). After histopathologic examination, one patient (Case 5) was found to have amebiasis, although hardly visible brown speckles were observed via endoscopy.

Two patients (18%) had pancolonic involvement with diffuse discoloration of the colonic mucosa. Our index patient (Case 10) had a heavy brown discoloration and

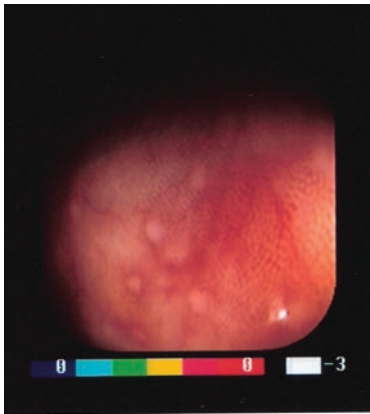
**Figure 1.** Heavy brown discoloration and reticulated pattern in the colonic mucosa.



**Figure 2.** Hardly visible speckles in the colonic mucosa.



**Figure 3.** White plaques suggestive of adenoma are easily distinguished against dark colored mucosa.



reticulated pattern in the colonic mucosa (Figure 1). The other patient with pancolonic involvement had diffuse light brown discoloration and scattered oval-shaped white areas measuring around 2 mm, suggesting adenoma formation; however, histology analysis showed no adenoma. Both patients had a history of long-term use of senna-containing teas (at least twice

a day). The rest of the patients (82%) had proximal disease, which was confined to the caecum and ascending colon. Endoscopic features of these patients were less pronounced when we compared them to diffuse involvement. In particular, hardly visible speckles (Figure 2) required special attention for diagnosis. Only 3 patients (27%) had this type of involvement; however, one patient was overdiagnosed with MC based on an initial assumption that the unhealthy appearance was due to MC, which was later found to be due to amebiasis. Overall, 7 patients (64%) had a very mild form of MC. White plaques suggestive of adenoma (Figure 3) were found endoscopically in 2 patients (18%), but only one flat adenoma was identified. This observation may be due to sampling error.

Clinical characteristics and found etiologic causes are summarized in Table 1. A total of 11 patients were identified as having MC and asked about the use of CAM practices. Only one patient (9%) had a history of long-term use of anthracene-containing laxatives. One patient (9%) denied any use of laxative drugs or herbal teas. The rest of the patients (n = 9, 81%) used *Cassia angustifolia* teas. The reasons given for herbal

**Table 1.** Patients' demographical features, colonoscopy indications and any laxative use.

Case	Age	Gender	Colonoscopy indication	Laxative
1	59	F	Constipation, bloating	-
2	55	F	Constipation	-
3	50	F	Constipation	+ Senna 2 yrs
4	47	F	Constipation rectal pain and rectal bleeding	-
5	47	F	Diarrhea	-
6	55	M	Change in bowel habits	-
7	55	F	Surveillance	-
8	46	F	Change in bowel habits	-
9	48	F	Change in bowel habits	-
10	79	F	Diarrhea	-
11	50	F	Constipation	-
12	56	M	Constipation	-

**Table 2.** Type of herbal remedies, duration of use.

Case	Herbal remedy	Reason	Duration	Still using	Any benefit	Side effects
1	Senna Tea	Bloating	2 yrs	Y	Y	Diarrhea
2	Senna Tea	To Lose weight	4 mos	N	N	Dyspepsia
3	No	N/A	N/A	N/A	N/A	N/A
4	Senna tea	constipation	1 yr	Y	N	N
5	Senna tea	Bloating	6 mo	Y	N	N
6	Senna tea	Bloating	1 yr	N	N	N
7	Senna tea	Habitual	4 yr	Y	N/A	N
8	Senna tea	To regulate bowel movements, bloating	6 mo	Y	N	N
9	Senna tea	Constipation	2 yr	Y	N	N
10	Senna tea	To regulate bowel movements, bloating, habitual	10 yrs	Y	Y	Diarrhea
11	Senna tea	Constipation	6 yrs	Y	N	N
12	No	N/A	N/A	N/A	N/A	N/A

Y: Yes, N: No, N/A: Not applicable

**Table 3.** Distribution, characteristics and histologic diagnosis of patients.

Case	Distribution	Pattern	Histology
1	Caecum	Hardly visible speckles	Melanosis coli (MC)
2	Caecum	Mild discoloration	MC
3	Caecum	Hardly visible speckles	MC
4	Caecum	Brown discoloration	MC
5	Caecum, ascending colon	Hardly visible speckles	Amebiasis, no pigment laden macrophages
6	Caecum	Granulation and discoloration	MC
7	Pancolonic	Diffuse discoloration and white areas	MC but no adenoma found
8	Caecum, ascending colon	Diffuse discoloration	MC
9	Caecum, ascending colon	Brown speckles	MC
10	Pancolonic	Reticulated, heavy Brown discoloration	MC
11	Caecum, ascending colon	Light Brown discoloration, white areas	MC with adenoma
12	Caecum	Light Brown discoloration	MC

remedy use were as follows (Table 2): constipation, bloating, losing weight, and habitual usage. Not all of the patients informed their doctor about CAM use during the thorough history taking, but all of them mentioned the ingestion during the interview. None of them had enough knowledge of the side effects.

Duration of usage is between 4 months to 10 years. Only 2 of the patients declared any benefit, and 4 patients were still using the teas. All the patients using herbal remedies relied on information from friends and family.

Endoscopic appearance, distribution and histological diagnosis of patients are outlined in Table 3.

## 4. Discussion

The term *melanosis* (Greek: *melas*, black; *osis*, condition) refers to conditions in which there is an abnormal grayish black or brownish black pigmentation

of an organ. The term only implies that the pigment is brown, not specifically melanin. MC is an abnormal brown or sometimes black pigmentation of the colonic mucosa due to long-term anthranoid laxative use. It was first described by Cruveilhier, and Virchow used the term *melanosis coli*. Early histochemical examinations suggested the pigment deposited is melanin or a melanin-like substance, although in the past microscopists repeatedly reported that no pigment is seen in the mucosa except in submucosal macrophages. It is true that most of the pigment granules do lie in the submucosa. The wall of the colon may appear grossly normal, but microscopic examination may show areas of pigment. Histologically, the epithelial cells are unremarkable. The mucosa and submucosa are usually edematous and contain pigment-laden macrophages and some plasma cells and mast cells [10].

The anthraquinones often occur in plants in the form of glycosides and have colors ranging from yellow to red.

These compounds are found in rhubarb root, senna leaf, pod, cascara sagrada, frangula, and aloe plants [1,11].

An active derivative, rhein, is formed in the large intestine by bacteria, which causes injury to the cells in the lining of the intestine and leads to apoptosis. The apoptotic cells appear as darkly pigmented bodies that are taken up by macrophages. When sufficient cells have been damaged, the distinctive pigmentation of the bowel wall develops [1,11-13].

MC has no specific symptom on its own; instead, symptoms may be attributed to such accompanying conditions as chronic constipation or diarrhea. We found chronic constipation, changes in bowel habits and diarrhea in 1 patient. This patient had been using the herbal tea for bloating and was aware of neither the side effects nor that this tea was the cause of her chronic diarrhea.

The intensity of the discoloration may differ from barely discernible brown coloration to black. Close examination may reveal small (2 mm to 1 cm) raised areas separated by a thin unpigmented reticulum (“toad back” appearance) [10]. In our cohort we have seen discoloration in the colon varying from barely noticed speckles to heavy dark brown. Because of the nature of the changes, it is easy to recall MC in a patient with diffuse heavy discoloration. During colonoscopy, special attention is given to mucosal integrity or irregularity, submucosal vessels, and changes in the colonic lumen. We also examine the color of the mucosa (such as redness or pallor) for clues to any underlying disease. Due to time constraints, discoloration may be overlooked if it is suggestive of benign causes. Inadequate bowel cleansing may be another factor contributing to not identifying the discoloration of MC.

In humans, and likewise in guinea pigs, macrophages are most abundant in the caecum, decreasing towards the rectum. This explains why the most frequent sites of involvement are the caecum and the appendix, which is the usual distribution pattern of MC, in the proximal as opposed to the distal colon, though it may affect the whole length of the large bowel [10,14].

We had only two patients with the diffuse form affecting the whole length of the colon. Other patients had proximal involvement as expected. Most of them were confined to the caecum and ascending colon. Long-term use of herbal remedies was believed to be a cause in one patient, while another one had been using laxatives for several years. If intake of herbals is stopped, the mucosal color returns to normal after almost a year. Some of the patients were not using herbals during the colonoscopy, though the time of cessation was not requested. For some of the patients with light brown speckles, discontinuation of the

offending agent and healing mucosa could be the cause.

Anthraquinone compounds are present in many over-the-counter laxatives, including herbal medicines. In addition, laxatives are frequently used as slimming agents, usually in the form of herbal teas. With a sufficient dose and duration of laxative ingestion, the entire colon may be involved. MC can be developed in as short as 6 weeks. In this cohort, most of the patients were short-term users (from 3 months to 3 years), whereas the history of laxative use was 10 years in a patient with diffuse involvement, which supports the argument that long-term use of senna-containing herbal teas could lead to development of MC. Laxative drug use was rare in our patient group, but 10 out of 11 patients admitted the use of herbal medicine for various reasons.

A study from Turkey investigated the 13 different preparations of diet-form teas, which could be accessed easily for their herbal components. Senna was the most commonly used plant in the herbal-form tea preparations marketed in Turkey. Some of the preparations also contain aloe, which increases the amount of anthraquinone more than desired [8]. There is no study investigating the incidence of CAM use in Turkish patients with gastrointestinal disorders. Most of the Turkish literature on CAM use is focused on cancer patients.

*Cassia angustifolia* is also known as “sena maki” among Turkish people, and extracts (liquid or solid) are used. Leaflets of senna contains at least 2.5% of hydroxyanthracene glycosides in the form of sennosides A and B [14]. Tea of senna was ingested regularly by 10 patients. The shortest duration of use that was enough for the development of MC was 3 months.

The use of CAM has been on the rise in the past few decades. Almost half of patients with gastrointestinal disorders have tried some form of CAM. CAM use appears to be more common in the functional gastrointestinal disorders. Patients with chronic and refractory gastrointestinal disorders tend to use more common and herbal products as the most frequent type of CAM. Overall, 10% of herbal therapy is used for digestive symptoms. Indeed, up to 30% of patients with chronic liver disease and 40% of patients with irritable bowel syndrome claim to have used some form of herbal medication [5-7].

Usage appears to be most common in patients with inflammatory bowel disease (IBD). Several studies have shown that female gender is most predictive of CAM use [4,15-17]. Patients are more likely to use CAM as an adjunct to conventional medicine than instead of conventional medicine, and only 48% of patients taking CAM provide this information to their physician.

Interestingly, doctors may not question patients about CAM usage [7].

MC has been reported as a consequence of long-standing IBD [7]. The authors concluded that chronic colitis with increased apoptosis could also cause MC without laxative abuse [18]. We did not have a patient with inflammatory bowel disease; one patient had a hardly visible brown discoloration in the caecum. Biopsy showed mild inflammation, but no pigment-laden macrophages were seen. Patients with IBD tend to use CAM therapies more frequently, which may be the reason why patients with IBD and MC should be questioned for the use of CAM.

Some investigators have suggested that increase in apoptosis of colonic mucosa by anthraquinone laxatives increased the risk of colonic cancer. However, recent data, including those from large-scale retrospective, prospective and experimental studies, did not show any increased cancer risk. It is widely accepted that increase in the incidence of adenomas is probably due to easier detection of small adenomas against the black background [2,19-21]. We had only one patient with adenoma and did not see any MC in proximal segments of patients with colon cancer.

Almost all of the patients in this study used herbal teas for gastrointestinal symptoms. Some of them showed serious side effects of laxatives like diarrhea. Patients were neither asked about herbal medicine use nor did they share this information with their primary physician.

*Limitations of the study.* This study was limited by recruiting patients with findings suggestive of MC; therefore, there was no control group to compare with. Although patients included in this study were selected in a prospective manner and asked about CAM and herbal tea usage, we did not investigate the patients with regular CAM use. The findings may therefore have generalization limited to patients consuming herbal teas regularly.

Secondly, neither was other patients undergoing regular colonoscopy asked nor did they specify whether

they used CAM therapies for their bowel problems. As we have no data on microscopic MC, we cannot exclude selection bias. The associations between CAM use and bowel disorders are therefore tentative. An additional limitation is the dependence on self-reporting for CAM.

## 5. Conclusion

It is important to emphasize that, particularly in regards to herbal treatments, “natural” or “alternative” is not equivalent to “safe.” Side effects, toxicities, and drug-herb interactions can occur, and patients should be made aware of this possibility. MC is a harmless mucosal discoloration due to anthraquinone laxatives, which is found to be a common agent consumed in high amounts in herbal tea.

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## Authors' contribution

TK made the study design, acquisition, analysis, interpretation of data and wrote this article. YB has been involved in revising in critically important content.

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TK works as consultant in gastroenterology in Hacettepe University School of Medicine and has special interest in diagnostic and therapeutic endoscopy

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