receptors in a clinical situation, because these substances should be not only effective but also well-tolerated and safe for long-term treatment. From these standpoints, a strategy using common food materials, such as lemon grass, instead of antibodies or synthetic substances appears to be promising. As lemon grass has been used in Asian foods for many years, its safety for daily intake appears to be guaranteed. Citral itself is used as a spice in many foods and its safety has also been proven by the investigation of National Toxicology Program of USA [15]. Moreover, citral has the advantage of suppressing both β7-integrin and CCR9 expression on lymphocytes in an RALDH2-specific manner. SAMP1/Yit mice we used in this study are very nice model for CD. Chronic sustained inflammation is not reproducible in a chemically induced model. However, for treatment study, treatment of mice for a long time is needed. Citral itself is vulnerable to oxidation, thus blending citral into diet chow will result in a decrease in the concentration of the active form of citral. Dissolving citral in drinking water is difficult due to its lipophilicity. Intraperitoneal injection of citral for a long period has an ethical problem and also may influence disease activity by stress. On the other hand, lemon grass tea drinking is a common habit for Asian people and is good way to ingest citral stably.

One concern we have is that lemon grass might reduce lymphocyte recruitment to levels lower than expected. Actually, vitamin A deficiency has been shown to cause attenuation of T cell recruitment to intestinal mucosa in a physiological condition [9], and vitamin A deficiency can cause many diseases, such as infectious colitis, respiratory infections and night blindness, as well as decrease in growth rate and slow bone development [26,27]. However, treatments for two weeks did not show any significant difference in weight gain or general appearance between mice with lemon grass treatment and control mice. Moreover, in our preliminary study, we also confirmed that even long-term treatment with lemon grass (35 weeks) did not produce any significant changes in body weight, small intestinal weight and length, sizes of Peyer's patches and MLNs in AKR/J mice (data not shown), suggesting that lemon grass did not have any toxic effect at the concentration used.

We speculated that the anti-inflammatory effect of lemon grass on ileitis is due mainly to inhibition of aberrant lymphocyte homing through attenuation of up-regulation of gut-homing molecules on the surface of lymphocytes, as we did not observe a direct effect of lemon grass on RALDH mRNA expression in DCs or MAdCAM-1 expression in the microvascular endothelium in this study. However, we cannot exclude the possibility that lemon grass is able to exert an inhibitory effect on immunological components of the intestinal immune system other than lymphocytes. It is also well known that lemon grass antimicrobial activity against bacteria or fungi. Therefore, there is also the possibility that microbacterial activity of lemon grass changes the population of commensal bacteria, leading to attenuation of inflammatory activity of ileitis. We previously showed enterobacteria recruitment of lymphocytes by modulating expression of adhesion molecules [28]. In addition, change in bacterial flora by prebiotics treatment altered lymphocyte homing [16]. Thus, it is also possible that lemon grass tea inhibits aberrant lymphocyte migration through modulating bacterial flora. Further studies are needed to determine the mechanism by which this natural herb prevents the development of ileitis and to explore its therapeutic usefulness for human IBD.

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