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Research Article

Biochemical Effects of Chamomile Oil on Inflammatory Biomarkers in Gastroenteritis

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Abstract

Gastroenteritis is a major health problem, especially in developing countries including Egypt. Chamomile has been used in the traditional medicine for the management of gastrointestinal disorders. The aim of this study was to evaluate biochemical alterations of inflammatory biomarkers in gastroenteritis after administration of chamomile oil. In order to achieve this aim 30 male albino rats was divided into two main groups, healthy control group and induced gastroenteritis group by using enteropathogenic E. coli. Half of them kept as positive control and the remaining treated with chamomile oil. The results of the present study showed a significant association between exposure to bacterial gastroenteritis and high level of inflammatory biomarkers like IL2, IL6, TNF, histamine and cortisol. The results also showed a significant decrease in inflammatory biomarkers IL2, IL6, TNF, histamine and cortisol in gastroenteritis group upon administration of chamomile oil. These findings suggested that chamomile oil possess anti-inflammatory activity confirming their traditional use.

Keywords: Gastroenteritis; Chamomile oil; Inflammatory biomarkers

Introduction

Acute gastroenteritis is a major health problem in hospital care and represents a major cause of morbidity and mortality worldwide especially in developing countries [1]. Acute gastroenteritis is a clinical syndrome refers to inflammation of the lining of both the stomach and small intestines caused by a variety of viral, bacterial, and parasitic enteropathogens [2].

Viruses that cause gastroenteritis include rotavirus, norovirus, adenovirus and astrovirus [3] while the most common types of bacteria causing gastroenteritis are *Salmonella, Shigella, Escherichia coli,* and *Campylobacter*. When food contaminated with bacteria and remains at room temperature for many hours, the bacteria can multiply and increase the risk of infection [4].

A number of protozoa can cause gastroenteritis, including *Giardia lamblia, Cryptosporidium* and *Entamoeba histolytica*. Poisoning with heavy metals can cause gastroenteritis e.g., arsenic and cadmium; also, seafood, e.g., ciguatera, scombroid and toxic encephalopathic shellfish poisoning [5].

Herbal medicine is widely used in the world and the majority of people in developing countries depend on it [6]. One of these medicinal plants is chamomile (*Matricaria chamomilla L.*), which belongs to the Asteraceae family. This plant is used in traditional medicine to treat ulcers, wounds, eczema and various gastrointestinal disturbances including diarrhea and vomiting [7].

Phytochemical analysis of chamomile flowers reflect presence of many phenolic compounds related to flavonoids apigenin, patuletin, luteolin, quercetin, it also contains terpenoids, chamazulene and sequiterpenes [8].

Objective of the Research

The main objective of the present study was to evaluate biochemical alterations of inflammatory biomarkers in gastroenteritis after administration of chamomile oil.

Materials and Methods

Healthy adult male albino rats, 8-10 weeks old, and average body weight 150-200 gm were used in the experimental investigation of this study. Rats were obtained from the Laboratory Animals Research Center, Benha University and used in accordance with the local ethics committee of Benha University for the use and care of animals in accordance with the NIH recommendations.

Animals were housed in separate metal cages, exposed to good ventilation, humidity and to a 12 hr light/dark cycle. Fresh and clean drinking water was supplied ad-libtium. Constant supplies of standard pellet diet, fresh and clean drinking water were supplied ad-libitum.

The animals were left for 15 days for acclimatization prior to the beginning of the experiment, and kept at constant environmental and nutritional conditions throughout the period of the experiment.

Rats are randomly divided into two main groups, placed in individual cages and classified as follow:

Group one (Control group): consist of 10 male rats, were fed on normal diet and fresh, clean drinking water. Kept as control group.

Group two (gastroenteritis group): consist of 20 male rats were fed on normal diet and water contaminated with 2 ml of enteropathogenic *E. coli* (1×10^9 colony forming units of *E. coli* per gram) for 10 days to produce bacterial gastroenteritis**.** Half of rats kept as positive control group and the remaining 10 rats subjected to oral administration of chamomile oil (0.5 ml/kg) for 3 weeks.

Blood sampling

Blood samples were collected from medial canthus of the eye of all animal groups in dry, clean screw capped tube, separated and centrifuged at 2500 rpm for 15 mins. The clean, clear serum was separated by Pasteur pipette and kept in a deep freeze at -20 C until used for determination of Tumor necrosis factor-α (TNF-α), Interlukin-1 (IL-1), Interlukin-6 (IL-6), Histamine, Cortisol.

Statistical Analysis

All values were expressed as mean ± standard error (SE). All statistical analyses were performed using SPSS (version 19). Statistical

differences among the experimental groups were assessed by ANOVA. Duncan's test was used as a follow-up test and significance was defined at $p<0.05$.

Results

The mean value of serum histamine level in gastroenteritis group was significantly increased ($P<0.05$) on comparison with healthy control group. The mean value of serum histamine level of chamomile treated group was significantly increased ($P<0.05$) on comparison with healthy control and significantly decreased ($P<0.05$) on comparison with gastroenteritis group (Table 1).

The mean value of serum cortisol level in gastroenteritis group was significantly increased ($P<0.05$) on comparison with healthy control group. The mean value of serum cortisol level of chamomile treated group was significantly increased ($P<0.05$) on comparison with healthy control and significantly decreased ($P<0.05$) on comparison with gastroenteritis group (Table 2).

The mean value of serum (IL2) level in gastroenteritis group was significantly increased ($P<0.05$) on comparison with healthy control group. The mean value of serum (IL2) level of chamomile treated group was non-significantly increased ($P<0.05$) on comparison with healthy control and significantly decreased ($P<0.05$) on comparison with gastrointestinal group (Table 3).

The mean value of serum (IL6) level in gastroenteritis group was significantly increased ($P<0.05$) on comparison with healthy control group. The mean value of serum (IL6) level of chamomile treated group was significantly increased ($P<0.05$) on comparison with healthy control and significantly decreased ($P<0.05$) on comparison with gastroenteritis group (Table 4).

The mean value of serum (TNFα) level in gastroenteritis group was significantly increased ($P<0.05$) on comparison with healthy control group. The mean value of serum (TNFα) level of chamomile treated group was significantly increased ($P<0.05$) on comparison with healthy control and significantly decreased ($P<0.05$) on comparison with gastroenteritis group (Table 5).

Discussion

Colic, diarrhoea and vomiting are the most common signs of gastrointestinal disorder. In developing countries, bacterial enteropathogens consider as the major cause of diarrhoeal diseases. Diarrhoeogenic *Escherichia coli* (enteropathogenic, enterotoxigenic, enteroinvasive and enterohaemorrhagic) is the most important group [7].

Our data showed that the mean value of serum histamine, IL2, IL6, Cortisol and TNFα levels in gastroenteritis group was significantly increased ($P<0.05$) on comparison with healthy control group.

Our results was in agreement with Gotts et al. [9] who reported that, in tissue infection, macrophages recognize pathogen-associated molecular patterns and release proinflammatory cytokines. These include granulocyte colony stimulating factor, IL-1a, IL-6, IL-12, and tumor necrosis factor a (TNF-α).

Chen et al. revealed that measurements of cytokines concentration used as clinical biomarkers to determine and identify the type of causative agent in gastroenteritis whether is a bacterial or viral [10]. Several proinflamatory cytokines have been evaluated from serum specimens, including interleukins (IL-6, IL-8), interferon (IFN-α, IFN-γ), and tumor necrosis factor-α (TNF-α). These cytokines play an important role in immunological response to various pathogens.

Several studies have focused on the use of cytokines for the diagnosis of bacterial versus viral gastrointestinal infections. Yeung et al. found a significant increase in serum concentration of IL-6, IL-8, INF-α, and TNF-α in patients with bacterial infections compared with viral infections [11]. However, evaluation of INF-α and TNF-α in serum was much less sensitive and specific for differentiation of bacterial from viral gastrointestinal infections. These findings regarding IL-6 are similar to other reports with smaller cohorts, which reported high sensitivity and specificity of IL-6. The use of serum IL-8 was also found to be less sensitive and specific for pathogen type discrimination [12].

In addition, Gonzalez et al. found that, serum concentrations of IL-10 in two separate studies was significantly elevated in patients with either bacterial or viral infections relative to healthy controls, but did not reliably discriminate between viral and bacterial infections [13].

Moreover, Yeung et al. analyze small group (17 patients with viral gastroenteritis and 14 patients with bacterial gastroenteritis) illustrated that serum TNF-α concentrations were high sensitive and specific for distinguishing between pathogens [12].

Our result was in agreement with Ting et al. who revealed that the plasma level of TNFα in children with diarrhea was higher than that in uninfected controls [14]. This may suggest that TNFα may continue to increase during a prolonged episode of bacterial gastroenteritis due to increase expression of TNFα in bacterial gastroenteritis.

Furthermore, Reuven et al. [15] indicate that TNFα plays an important role in host defense against bacterial gastroenteritis and indicated the presence of bacterial infection with high sensitivity and specificity so, it can be a useful biomarker for differentiating between bacterial and viral gastroenteritis in acute phase illness.

Histamine is an autacoidal neurotransmitter and widely distributed in biological tissues. It is an important mediator in the process of inflammation. Mast cells consider as important source of histamine release. In the infective disease, bacterial products may also act as histamine liberators through immunological (IgE-mediated) and non-immunological response [16].

Chen et al. revealed that, *Salmonella typhi* can liberate gastric histamine from mast cells causing hemorrhagic ulcer, also, *Escherichia coli* can produce damage in gastric mucosa through enhancing histamine secretion and oxyradical generation [17]. Histamine may cause increase in gastric mucosal permeability to electrolytes and

Group	Period (week)			Mean
	1	2	3	
Healthy control group	2.11 ± 0.26^{cA}	2.19 ± 0.36^{cA}	2.89 ± 0.19^{dA}	2.40 ± 0.18^{d}
Gastroenteritis group	13.93 ± 1.72^{aC}	19.27 ± 0.89^{aB}	28.06 ± 3.25^{aA}	20.42 ± 2.09^{a}
Chamomile treated group	10.45 ± 0.3^{bA}	10.31 ± 0.34^{bA}	10.54 ± 0.31^{cA}	10.43 ± 0.17^{c}

a, b & c: There is no significant difference ($P>0.05$) between any two means, within the same column have the same superscript letter.
A, B & C: There is no significant difference ($P>0.05$) between any two means for the same attribute, within the same row have the same superscript letter.

Table 1: The mean values ± S.E of serum (Histamine) in healthy control, gastrointestinal, gastrointestinal with chamomile groups.

Group	Period (week)			Mean
	1	2	3	
Healthy control group	7.36 ± 0.37^{cA}	7.25 ± 0.40^{dA}	7.41 ± 0.33^{dA}	7.34 ± 0.19^{d}
Gastroenteritis group	51.61 ± 6.54^{aC}	73.08 ± 3.56^{aB}	81.10 ± 3.33^{aA}	68.60 ± 4.49^{a}
Chamomile treated group	22.21 ± 1.55^{bB}	22.03 ± 1.07^{cB}	28.78 ± 1.62^{cA}	24.34 ± 1.21^{c}

a, b & c: There is no significant difference (P>0.05) between any two means, within the same column have the same superscript letter.
A, B & C: There is no significant difference (P>0.05) between any two means for the same attribute, within the same row have the same superscript letter.

Table 2: The mean values ± S.E of serum (Cortisol) in healthy control, gastrointestinal, gastrointestinal with chamomile groups.

Group	Period (week)			Mean
	1	2	3	
Healthy control group	0.51 ± 0.14^{bA}	0.28 ± 0.06^{dA}	0.36 ± 0.11^{cA}	0.38 ± 0.06^{c}
Gastroenteritis group	1.17 ± 0.26^{aC}	3.19 ± 0.44^{aB}	3.87 ± 0.27^{aA}	2.74 ± 0.39^{a}
Chamomile treated group	0.42 ± 0.03^{bA}	0.69 ± 0.05^{cA}	0.61 ± 0.10^{cA}	0.57 ± 0.05^{c}

a, b & c: There is no significant difference (P>0.05) between any two means, within the same column have the same superscript letter.
A, B & C: There is no significant difference (P>0.05) between any two means for the same attribute, within the same row have the same superscript letter.

Table 3: The mean values ± S.E of serum (IL2) in healthy control, gastrointestinal, gastrointestinal with chamomile groups.

Group	Period (week)			Mean
	1	2	3	
Healthy control group	6.48 ± 0.46^{bA}	5.88 ± 0.86^{cA}	5.82 ± 0.55^{cA}	6.06 ± 0.35^{c}
Gastroenteritis group	15.39 ± 2.02^{aB}	40.12 ± 1.72^{aA}	42.51 ± 2.78^{aA}	32.67 ± 3.87^{a}
Chamomile treated group	10.33 ± 0.66^{bC}	24.27 ± 1.67^{bB}	33.23 ± 3.01^{bA}	22.61 ± 3.03^{b}

a, b & c: There is no significant difference (P>0.05) between any two means, within the same column have the same superscript letter.
A, B & C: There is no significant difference (P>0.05) between any two means for the same attribute, within the same row have the same superscript letter.

Table 4: The mean values ± S.E of serum (IL6) in healthy control, gastrointestinal, gastrointestinal with chamomile groups.

Group	Period (week)			Mean
	1	2	3	
Healthy control group	31.21 ± 2.17^{cA}	33.19 ± 2.15^{dA}	30.20 ± 5.02^{dA}	31.53 ± 1.81^{d}
Gastroenteritis group	64.85 ± 6.07^{aC}	89.46 ± 6.08^{aB}	107.77 ± 10.72^{aA}	87.36 ± 6.73^{a}
Chamomile treated group	39.38 ± 4.43^{cC}	56.63 ± 6.01^{cB}	65.84 ± 6.33^{cA}	53.95 ± 4.43^{c}

a, b & c: There is no significant difference (P>0.05) between any two means, within the same column have the same superscript letter.
A, B & C: There is no significant difference (P>0.05) between any two means for the same attribute, within the same row have the same superscript letter.

Table 5: The mean values ± S.E of serum (TNFα) in healthy control, gastrointestinal, gastrointestinal with chamomile groups.

renders the stomach more liable to acid induced damage.

Furthermore, Hung et al. [16] demonstrated that histamine may cause a potent contraction of the smooth muscle cells and gastric mucosal internal leak that may contribute to plasma protein, electrolyte and water loss.

Verbrugghe et al. [18] hypothesized that cortisol plays a role in the stress related to infection with *Salmonella typhi* through activation of sympathetic nervous system and hypothalamic pituitaryadrenal axis, resulting in the release of catecholamines and glucocorticoids. These stress hormones can affect the host immune response, but the pathogenesis of an infection can also be altered by direct effects of these stress mediators on the bacteria [19].

Our result showed that the mean value of serum histamine. IL2, IL6, Cortisole and (TNFα) levels of chamomile treated group was significantly increased (P<0.05) on comparison with healthy control and significantly decreased (P<0.05) on comparison with gastroenteritis group.

Chamomile has been used for decades as a medicinal plant in the form of herbal tea for gastrointestinal problems due to its anti-inflammatory and analgesic properties [7].

Several constituents of chamomile including phenolic compounds such as apigenin, luteolin, quercetin, myricetin, rutin, terpenes like chamazulene, α-bisabolol and tannin compounds have been studied regarding their anti-inflammatory activities [20].

In accordance with our data, McKay et al. revealed that, chamazulene, α-bisabolol, and apigenin exhibit the highest anti-inflammatory activity against pro-inflammatory agents [21].

Many phenolic components of plant source, especially flavonoids, possess anti-inflammatory, anti-carcinogenic and free radical scavenging properties and the number of molecules isolated and characterize continues to increase [22]. Previous studies have demonstrated that individual constituents of chamomile such as chalmuzene, luteolin and apigenin are effective in inhibiting COX-2, iNOS and leukotrine expression in cell culture [21].

Furthermore, Srivastava et al. [23] shown that, chamomile preferentially inhibit COX-2 and mechanisms of action of chamomile resemble those of NSAIDs, which have been demonstrated to possess chemopreventive properties by their common ability to inhibit prostaglandin synthesis.

In addition, Sebai et al. [24] reported that tannins provides a significant protection from mast cell degranulation and also significant decrease in the release of allergic mediators like blood histamine and possess mast cell stabilizing, anti-allergic and anti-histaminic activities. Also, tannins can denature protein to form protein tannate complex which makes the intestinal mucosa more resistant and reducing its secretion.

More recently, Mohamed et al. [25] demonstrated that chamomile decoction extract protects against ethanol-induced gastric mucosal damage. The gastroprotection offered by chamomile may be related partly to gastric mucosa sulfhydryls safety as well as its antioxidant properties and opposite effect on some intracellular mediators such as free iron, hydrogen peroxide and calcium.

Also, Roberts et al. [26] showed that, chamomile exert spasmolytic activity by elevate cyclic nucleotides in the smooth muscle, leading to reduced calcium elevations and inhibition of contractility.

Conclusion

In conclusion, our result demonstrated that, bacterial gastroenteritis accompany by increased level of serum inflammatory biomarkers and clearly elucidate the protective effects of chamomile oil against bacterial induced gastroenteritis through decreasing inflammatory biomarkers and intestinal motility. These findings confirmed the basis for the use of chamomile extracts in traditional medicine for the treatment and/or management of digestive system disorders.

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