Phytochemical characterization of essential oils from plants of the genus Cinnamomum and their effect on diarrhea and disruption of the intestinal epithelium induced by 5-FU.

ABSTRACT

Aims: This article aims to evaluate the phytochemical characteristics and biological activity of Cinnamomum cassia Blume and Cinnamomum zeylanicum Blume essential oils, specifically their effects on weight loss, diarrhea, and epithelial damage in a murine model of 5-fluorouracil-induced intestinal mucositis.

Study design: The study consisted of a controlled experimental design using a murine model to evaluate the therapeutic potential of essential oils in intestinal mucositis induced by chemotherapy with 5-FU.

Study location: This research was conducted at the Medicinal Plant Research Center (NPPM), Federal University of Piauí, State of Brazil.

Methodology: The study included albino (swiss) musmuscullus mice weighing 30-40 g, divided into different groups (n = 7 per group) to analyze the effects of essential oils administered orally. Essential oils were extracted from the bark of Cinnamomum species and characterized using gas chromatography-mass spectrometry (GC-MS). Mucositis was induced using 5-fluorouracil (5-FU), and the effects of essential oils on animals were assessed by measuring animal body mass, diarrhea score, and assessing epithelial damage using lactate dehydrogenase release.

Results: The analysis showed that both oils contained predominantly cinnamaldehyde, with significant variation in phytochemical diversity. Treatment with essential oils attenuated weight loss and severity of 5-FU-induced diarrhea. Specifically, the highest dose (50 mg/kg/day) of both essential oils significantly reduced lactate dehydrogenase levels, indicating reduced epithelial damage. Statistical analysis was conducted using one-way ANOVA followed by Bonferroni's post-test, with results showing significant differences ($p < 0.05$) in treatment effects compared to the control group.

Conclusion: This study contributes to the theory that the observed beneficial effects of Cinnamomum cassia and Cinnamomum zeylanicum essential oils can be attributed to their distinct phytochemical compositions. While Cinnamomum zeylanicum oil exhibits greater phytochemical diversity, Cinnamomum cassia oil is characterized by a higher proportion of cinnamaldehyde, constituting approximately 80% of its composition. The more pronounced effects observed with Cinnamomum cassia oil may suggest a potential synergistic dynamic where high cinnamaldehyde content plays a critical role, highlighting the importance of specific concentrations of compounds to achieve therapeutic efficacy.

Keywords: Essential oils; Antineoplastic chemotherapy; phytochemistry; diarrhea

Comment [D1]: Italicize the scientific name

1. INTRODUCTION

Despite the significant advances in cancer treatment, patients often experience debilitating effects that have a significant impact on their quality of life. Gastrointestinal mucositis (GIM), also known as erosive gastropathy, is a serious complication that is characterized by inflammation and ulceration of the digestive system. In the most severe instances, GIM necessitates the suspension of chemotherapy, which further diminishes the patient's prognosis (Sousa et al., 2024).

Chemotherapy-induced intestinal mucositis is caused by the destruction of the intestinal epithelium. The initial insult triggers the apoptosis of epithelial cells and the release of pro-inflammatory cytokines, this creates a progression that amplifies the damage to the mucosa, ultimately causing severe intestinal pain and diarrhea. This not only adversely affects patientsquality of life, but also frequently impedes the adherence to the prescribed anti-cancer treatment protocols and their recommended intensity (Basile et al., 2019; Gobbo et al., 2024).

Currently, there is a lack of specific medications dedicated to preventing or curing mucositis, which opens a promising avenue for exploring natural products as potential therapeutic agents.

In this context, previous studies have demonstrated the antibacterial activity of plants *Cinnamomum* genus essential oil (Sousa et al., 2016). Further studies, such as Freire et al. (2014), have documented the activity of cinnamon against various microorganisms, this suggests that it may have a role in mitigating the chemotherapy-induced intestinal mucositis. Intestinal dysbiosis, which is characterized by a misbalanced microbiota composition, is associated with inflammation and can significantly increase the damage to the tissue (Hamouda et al., 2017; Gordon et al., 2024).

As a result, anti-inflammatory and antibacterial agents have the potential to reduce the degree of this condition. As a result, the current study was designed to evaluate the phytochemical characteristics and biological activity of essential oils from Cinnamomum cassia Blume and Cinnamomum zeylanicum Blume. Specifically, the research aims to assess their effects on weight loss, diarrhea, and epithelial disruption in a murine model of 5-fluorouracil-induced intestinal mucositis.

2. MATERIAL AND METHODS

2.1 Extraction and obtainment

The essential oils extracted from the bark of *Cinnamomum cassia* Blume and *Cinnamomum zeylanicum* Blume were imported from China and Sri Lanka, respectively (Yanih PROD Farm LTDA Lot: BRAFEV21 and Ferquima Químicos LTDA Lot: 219). Both oils had a purity level exceeding 99%.

2.2 Characterization of essential oils by gas chromatography coupled with mass spectrometry.

The chemical characterization of the essential oils from *Cinnamomum cassia* Blume and *Cinnamomum zeylanicum* Blume was conducted using a Shimadzu® gas chromatograph coupled with a mass spectrometer (GC-MS), model CGMSQP2010 SE, equipped with an AOC-5000 automatic injector (Shimadzu, Kyoto, Japan) and an SLB-5MS column (30 m × 0.25 mm × 0.25 µm). The analysis conditions were as follows: helium was used as the carrier gas at a flow rate of 1 mL/min, with an injector temperature set at 250°C. The temperature program included an initial temperature of 60 °C (held for 3 minutes), followed by a ramp rate of 3°C/min to a final temperature of 246 °C, maintained for 10 minutes. The detector temperature was 250 °C, and the injection volume was 1 µL. The mass spectrometry conditions involved single electron impact with a quadrupole ion detector (70 eV, mass range of 45 to 450 Da). Quadruplicate analyses were performed, and identification and relative quantification of components were performed based on the areas of corresponding chromatographic peaks and compared with databases and literature records (NIST), with a similarity of at least 95%.

2.3 Animals used in research and ethical aspects

All experiments were conducted in compliance with the Guidelines for the Care and Use of Laboratory Animals established by the Brazilian College of Animal Experimentation (COBEA) and the National Institutes of Health, Bethesda, MD, USA. This study was reviewed and approved by the Ethical Committee for Animal Experimentation (CEUA/UFPI/528/18). Euthanasia procedures adhered to Resolution 1000/2012 of the Federal Council of Veterinary Medicine. Female albino mice (Switzerland strain) weighing between 30 and 40 g were randomly assigned to groups of seven animals for statistical analysis (n = 7). Mice were obtained from the Bioterium of the Medicinal Plant Research center (NPPM) at the Federal University of Piauí. They were housed at a temperature of 25 ± 1 °C with a 12-hour light-dark cycle, provided with feed and water ad libitum. Animals were fasted for 6 hours prior to euthanasia. Euthanasia was performed via an overdose of

anesthetics (sodium thiopental 150 mg/kg and lidocaine 10 mg/kg, administered intraperitoneally).

2.4 (5-FU)-induced intestinal mucositis experimental model

Intestinal mucositis was induced by administering 5-fluorouracil (5-FU) at a dose of 50 mg/kg daily for 6 consecutive days according to Hamouda et al. (2017). Animals were treated (for 6 days) with cinnamon essential oil (CC) and *Ceylon cinnamon* essential oil (CZ) in a Tween/saline vehicle (polysorbate 80 0.1% + sodium chloride 0.9%) and administered by oral gavage (vo). The doses were 25, 50, and 100 mg/kg/day. On day 7, animals were euthanized according to a previously established anesthetic overdose protocol.

2.5 Diarrhea scoring

On the seventh day of the protocol, body weight and diarrhea score of animals were measured according to the criteria outlined by Kurita et al. (2000).

2.6 Determination of epithelial rupture by luminal release of Lactate Dehydrogenase

To measure epithelial rupture, the small intestines were washed with 3 milliliters of water, and the excess fluid was collected and centrifuged. The supernatant was obtained by a dry chemistry method using the Vitros 950 analyzer (Ortho-Clinical Diagnostics, Rochester, NY, USA).

2.7 Statistical Analysis

Results were expressed as the mean ± standard deviation for variables that followed a normal distribution. Statistical analyses were performed using one-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparison post-test to evaluate differences between groups. For non-parametric data, the Kruskal-Wallis test followed by Dunn's multiple comparison test was used. All analyses were conducted using GraphPad Prism 8.0 (Intuitive Software for Science, San Diego, CA), with a significance threshold set at $p < 0.05$ to indicate statistically significant diferences.

3. RESULTS AND DISCUSSION

The composition of the essential oils was characterized by identifying and quantifying the major secondary metabolites present. For *Cinnamomum cassia*, the analysis identified a total of six secondary metabolites, among which cinnamaldehyde and p-methoxycinnamaldehyde were the most prominent. These two compounds together account

for 93.7% of total composition of this essential oil. Cinnamaldehyde, in particular, is the most significant compound, constituting over 80% of the volatile components of the essential oil *Cinnamomum cassia*.

The analysis revealed a total of 13 secondary metabolites in the essential oil derived from *Cinnamomum zeylanicum*. This essential oil exhibits a significant chemical diversity, it is primarily composed of Cinnamaldehyde (82.8%), followed by (E)-caryophyllene (3.4%), linalool (1.3%) and citronelol acetate (0.9%. Additionally, 10 other compounds were identified, each contributing less than 2% to the overall composition of the essential oil. The secondary metabolites present in the essential oil of *Cinnamomum zeylanicum* and their relative abundances are detailed in Table 1-2.

The numerical data for each component of the essential oils demonstrates consistency across repetitions and highlights the predominance of cinnamaldehyde in both essential oils. Despite being primarily composed of cinnamaldehyde, the essential oil of *Cinnamomum zeylanicum* exhibits a more complex bioactive profile due to its diverse array of secondary metabolites compared to the essential oil of *Cinnamomum cassia* (Figure 1).

Figure 1: Comparison of the total ion chromatograms of the essential oils from Cinnamomum cassia and Cinnamomum zeylanicum. The chromatograms are presented with a standard retention time cut ranging from 5 to 33 minutes.

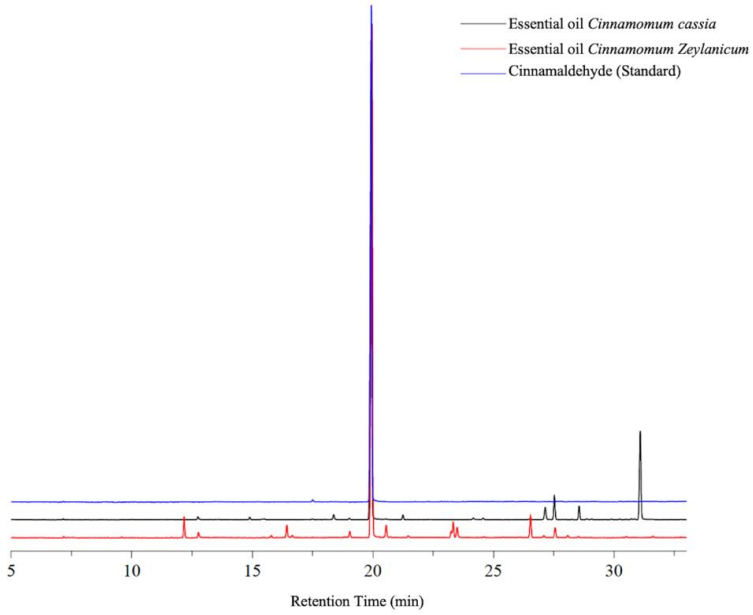


Table 1.Relative abundance and identification of chemical components in the essential oil of *Cinnamomum cassia* Blume

Retention time (min)	Compound	Main fragments	Relative Abundance (%)	standard deviation
18.371	2-methylbenzaldehyde	65, 77, 118, 136	0,65	18,04
19.929	Cinnamaldehyde	51, 77, 103, 131	80,68	10,27
27.143	Coumarine	63, 90, 118, 146	1,89	11,80
27.523	Cinnamyl acetate	92, 115, 133, 176	3,46	11,41
31.086	*p*-methoxycinnamaldehyde	91, 119, 131, 162	13,33	10,97

Legend: The percentages of the identified metabolites in the essential oil represent the average values obtained from four independent analyses.

Table 2. Relative abundance and identification of chemical components in the essential oil of *Cinnamomum zeylanicum* Blume

Retention time (min)	Compound	Main fragments	Relative Abundance (%)	standard deviation
12.170	Linalool	71, 93, 121, 136	2,29	1,95

12.763	2-Phenylethanol	51, 65, 91, 122	0,65	3,26
16.427	*α*-Terpineol	59, 93, 121, 136	1,57	2,27
19.044	Phenethyl acetate	51, 65, 91, 104	0,73	3,52
19.965	Cinnamaldehyde	51, 77, 103, 131	83,11	1,16
20.552	*E*-Anethole	77, 105, 117, 148	1,74	2,55
23.248	α-Terpinyl acetate	59, 93, 121, 136	0,87	2,79
23.330	Citronellyl acetate	69, 81, 95, 123	2,01	1,92
23.494	Eugenol	77, 103, 131, 164	1,43	1,93
26.534	*E-Caryophyllene*	69, 93, 133, 161	3,34	0,96
27.551	Cinnamyl acetate	92, 115, 133, 176	1,40	0,89
40.479	Benzyl benzoate	77, 91, 105, 212	0,85	3,14

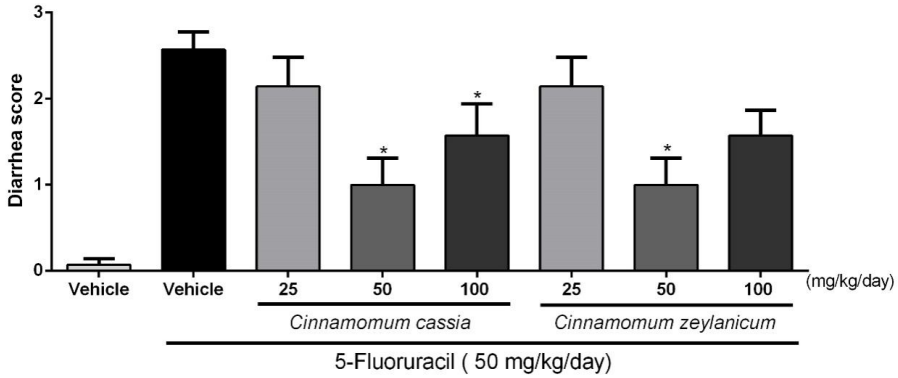
Legend: The percentages of the identified metabolites in the essential oil represent the average values obtained from four independent analyses.

In this study, animals treated with 50 mg/kg/day of 5-fluorouracil (5-FU) for 7 days, including those in the control group and those co-treated with essential oils of *Cinnamomum cassia* Blume (CC) and *Cinnamomum zeylanicum* Blume (CZ) at doses of 25, 50, and 100 mg/kg, exhibited a significant negative variation in body weight (-20.57 ± 4.4%). This indicates a loss of body mass associated with the 5-FU treatment.

However, the co-administration of CC and CZ essential oils resulted in a reduction in weight loss: CC at 25 mg/kg and 50 mg/kg doses mitigated weight loss by 17.9 ± 1.6% and 19.3 ± 5.4%, respectively ($p < .05$). Similarly, CZ attenuated weight loss by 21.5 ± 9% at the 50 mg/kg dose ($p < .05$).

The study demonstrated that mice treated with 5-fluorouracil (5-FU) exhibited a significant increase in the median diarrheal scores compared to mice in the saline control group ($p < .05$). However, essential oils of *Cinnamomum cassia* Blume (CC) and *Cinnamomum zeylanicum* Blume (CZ), administered at a dose of 50 mg/kg/day, were effective in mitigating the severity of diarrhea. This effect was observed through a reduction in the semi-quantitative diarrheal scores in animals with 5-FU-induced intestinal mucositis (Figure 2).

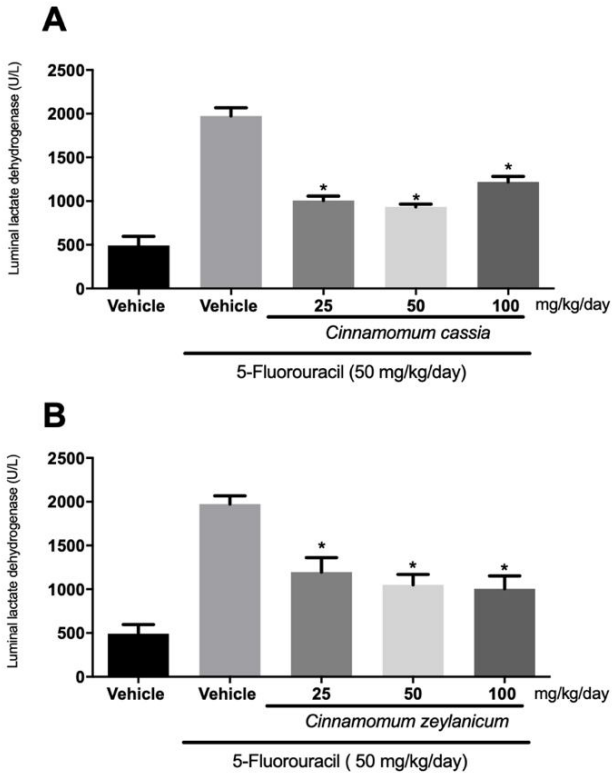
Figure 2 Effect of the essential oils of *Cinnamomum cassia* Blume and *Cinnamomum zeylanicum* Blume on diarrhea in animals with 5-FU-induced intestinal mucositis.



Legend: The figure illustrates the outcome of the analysis of the diarrhea scores of the mice in the different groups treated with the essential oils of *Cinnamomum cassia* and *Cinnamomum zeylanicum*, respectively. Data was expressed as the mean ± standard deviation. Percentage of weight variation. ANOVA was performed followed by Bonferroni's Multiple Comparisons Test. * $p < 0.05$, when compared to the vehicle + 5FU group.

In addition to assessing the structural effect of 5-fluorouracil (5-FU) on intestinal tissues, we also evaluated the chemical effects of essential oil administration on 5-FU-induced intestinal inflammation. The analysis of epithelial damage was conducted by measuring the lactate dehydrogenase (LDH) enzyme levels in the intestinal lumen. Treatment with 5-FU resulted in a significant increase in LDH content to 1973 ± 95 U/L compared to the control group, which had an LDH level of 493 ± 103 U/L. Conversely, administration of the essential oils reduced LDH release into the lumen, with levels maintained at 935.4 ± 31 U/L and 1052 ± 117 U/L at the highest dose (50 mg/kg/day) of *Cinnamomum cassia* (CC) and *Cinnamomum zeylanicum* (OCZ), respectively (Figure 3).

Figure 3- The effect of the essential oils of *C. cassia* Blume and *C. zeylanicum* Blume on the levels of lactate dehydrogenase in the intestinal lumen of animals with 5-FU-induced intestinal mucositis.



Legend: Sections A and B demonstrate the result of the release of the lactate dehydrogenase enzyme into the intestinal lumen of groups treated with the essential oils from *Cinnamomum cassia* [A] and *Cinnamomum zeylanicum* [B]. The data was expressed as the mean ± standard deviation. Lactate dehydrogenase levels in intestinal lavage were analyzed. Statistical analysis was conducted using ANOVA followed by the Bonferroni Multiple Comparisons Test * $p < 0.05$ when compared to the 5-FU + vehicle group.

The chemical evaluation of essential oils by gas chromatography linked to mass spectrometry helped in the characterization of these oils. The analysis unveiled a diversified profile of secondary metabolites in the essential oils, partly agreeing with the work of Firmino et al. (2018) for *Cinnamomum cassia* Blume and that of Singh et al. (2007) for *Cinnamomum zeylanicum* Blume. One of the major similarities that drew our attention to these two oils is the fact that cinnamaldehyde is the major compound in both species. Cinnamaldehyde comprises more than 70% of the volatile oil composition of both species, which is concurrent with the literature (Lee, Roberta; Balick, 2005). This compound was defined as a pleiotropic

bioactive agent, showing many beneficial effects related to the biological activity of cinnamon.Its known reactivity and a degree of chemical richness are at the base of its numerous beneficial features, comprising marked antimicrobial and anti-inflammatory activities (Autelitano et al., 2017, Silva et al., 2017; Wang, Kang, Kwon, 2021; Singh, Yadav et al., 2024; Zhao et al., 2024; Yan et al., 2024).

Chemotherapy-induced mucositis is characterized by an inflammatory process that plays a crucial role in the perpetuation of tissue damage (Hamouda et al., 2017; Kircadere et al., 2024). The search for therapies that modulate this inflammatory response is therefore essential. Essential oils, due to their complex composition of secondary metabolites, have the potential to modulate different biological pathways relevant to mucositis.

Essential oils, due to their complex composition of secondary metabolites, have the potential to modulate different biological pathways relevant to mucositis. Additional studies are needed to elucidate the specific mechanisms of action of these compounds (Figures 4 and 5) and determine whether they have anti-inflammatory effects that may be beneficial in the context of chemotherapy-induced mucositis.

The present investigation showed that essential oils had a significant effect on reducing the body mass loss of animals that were treated with 5-FU. This weight loss is considered the hallmark of the consumptive process in 5-FU-induced intestinal mucositis. It results from a combination of reduced food intake, impaired nutrient absorption due to inflammation in the intestinal wall, and fluid loss into the intestinal lumen, leading to altered fecal output. (Eduardo et al., 2018; Keefe, 2007).

The toxic effects of chemotherapies on the intestine, particularly with compounds like 5-FU that are antimetabolites, are caused by the destruction of the protective barrier of mucus that lines the intestine. This condition is traditionally referred to as mucositis, but it is now recognized as a complex process that involves both epithelial damage and the activation of the mucosal immune system, as well as the release of pro-inflammatory cytokines (Lee, Chun Seng; Ryan; Doherty, 2014; Logan et al., 2008). The small intestine's high rate of cellular regeneration causes it to be particularly susceptible to agents that inhibit the proliferation of cells, such as 5-FU, these agents negatively affect the maintenance of intestinal homeostasis and are therefore considered an antimetabolic agent. The inflammation associated with mucositis is caused by damage to both the epithelial and subepithelial components, these components include the Lieberkühn crypts and microvilli (Leocádio et al., 2015; Tsujii et al., 2023).

To assess the degree of epithelial damage, we used the lactate dehydrogenase (LDH) assay on the fluid excreted by the intestine, as described by Zanotto-Filho et

al.(2011). LDH, a cytosolic enzyme that is released during the lysis of cells, serves as a means of injury detection. While LDH data are potentially complex and sensitive, our results indicate that the treatment of 5-FU with essential oils may mitigate some of the epithelial harm caused by the chemical.

The observed beneficial effects of the essential oils from Cinnamomum cassia and Cinnamomum zeylanicum may be attributed to their distinct phytochemical compositions. While Cinnamomum zeylanicum oil exhibits a greater phytochemical diversity, Cinnamomum cassia oil is characterized by a higher proportion of cinnamaldehyde, constituting around 80% of its composition. This key compound, cinnamaldehyde, has been well-documented for its anti-inflammatory properties, which may stem from its ability to suppress pro-inflammatory gene expression and block macrophage activation (Kim et al., 2018; Ghardashpour et al., 2023). The more pronounced effects observed with Cinnamomum cassia oil could suggest a potential synergistic dynamic where the high cinnamaldehyde content plays a critical role, underscoring the importance of specific compound concentrations in achieving therapeutic efficacy.

4. CONCLUSION

These data indicate that the essential oils of Cinnamomum cassia and Cinnamomum zeylanicum have distinct chemical diversity and their biological activity in the 5-FU-induced musocyte model can be attributed to their distinct phytochemical compositions. While Cinnamomum zeylanicum oil exhibits a greater phytochemical diversity, Cinnamomum cassia oil is characterized by a higher proportion of cinnamaldehyde, constituting about 80% of its composition. The more pronounced effects observed with Cinnamomum cassia oil may suggest a potential synergistic dynamic where the high cinnamaldehyde content plays a critical role, highlighting the importance of specific concentrations of compounds to achieve therapeutic efficacy.

Comment [D2]: Check spelling

ETHICAL APPROVAL

All experiments were performed in accordance with the Guidelines for the Care and Use of Laboratory Animals, established by the Brazilian College of Animal Experimentation (COBEA) and in accordance with the guidelines of the National Institutes of Health, Bethesda, MD, USA. T This work was submitted to and approved by the Ethics Committee for Animal Experimentation of the federal University of Piaui (CEUA/UFPI/528/2018). Regarding euthanasia, all samples were collected and examined in accordance with the guidelines of the CONCEA (NR37) and Brazilian Federal Council of Veterinary Medicine (Resolution 1000/2012).

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