# Efficacy of Chamomile for Preventing Chemo- and Radiotherapy-induced Oral Stomatitis

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# How would Chamomile work?

## Oral mucositis is an inflammatory condition involving the oral mucosa.

With inflammation, there is an induced expression and enzyme activity of COX-2, which produces inflammatory mediators such as PGE2.

Chamomile, exerts its anti-inflammatory properties by inhibiting the production of PGE2 by the macrophages.

By inhibiting COX-2 gene expression and enzymatic activity, chamomile presumptively treats oral mucositis in patients receiving chemo- and radiotherapy

# Rationale

Oral mucositis affects the quality of life of cancer patients and results in treatment noncompliance or discontinuation. The clinical and economic consequences of OM include increased infections, complication, duration of hospitalizations, and costs. Alternative treatments which were studied include the use of naturally occurring compounds such as chamomile to their lower cost and lower adverse effects compared with chemical drugs.

# Objectives

## GENERAL OBJECTIVE

This systematic review aims to assess the efficacy of chamomile in preventing chemo- or radiotherapy-induced oral stomatitis

## SPECIFIC OBJECTIVES

This systematic review specifically aims to compare the efficacy of chamomile in preventing chemo- or radiotherapy-induced oral stomatitis vs. placebo, no treatment, or another active intervention, in terms of the following:

- Incidence
- Severity
- Adverse event

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# METHODOLOGY

## Screening

INCLUSION CRITERIA

- Patients of all age groups diagnosed with cancer scheduled for cancer treatment
- Use of chamomile alone or as adjunct to standard oral care for preventing oral mucositis in cancer patients
- Randomized controlled trials and previous systematic reviews

EXCLUSION CRITERIA

- Chamomile is used in conjunction with other treatments aside from standard therapy
- Chamomile is used in treating or preventing oral mucositis caused by conditions other than chemotherapy and radiotherapy

## Analysis

- RevMan 5.4.1
- Relative risk ratios with 95% confidence intervals
  - For dichotomous data
  - Significant if CI do not cross 1
- Mean differences with 95% confidence interval
  - For continuous data
  - Significant if CI do not cross 0

## Outcomes

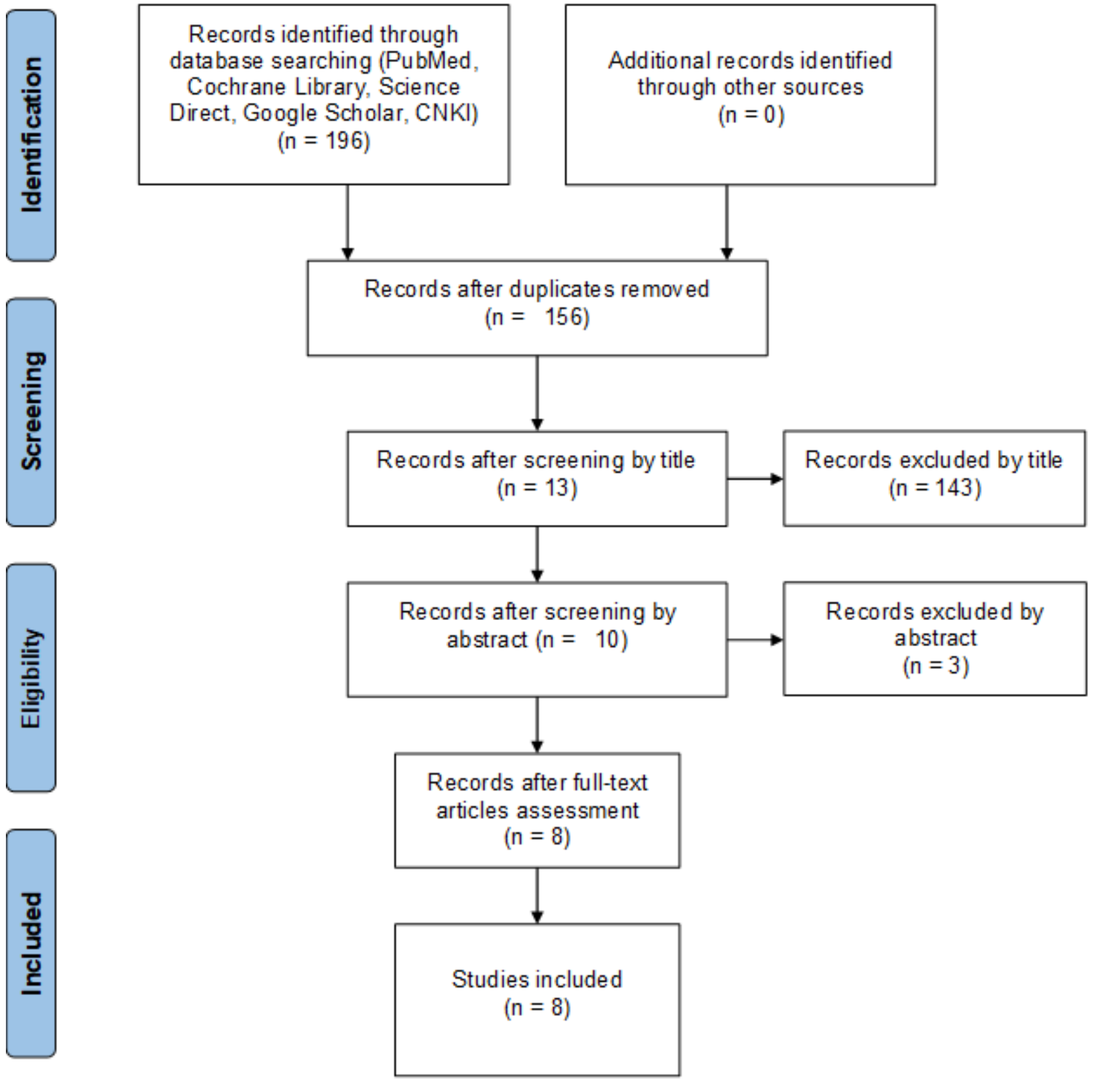
PRIMARY OUTCOME:

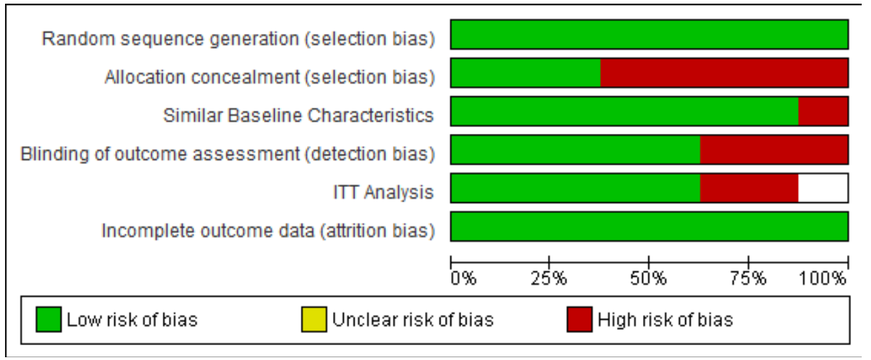
Change in incidence of oral mucositis (measured as the number of patients with ulcerations in the oral mucosa)

SECONDARY OUTCOMES:

- Severity
- Adverse event
- Duration of oral mucositis

# Quality of Included Studies



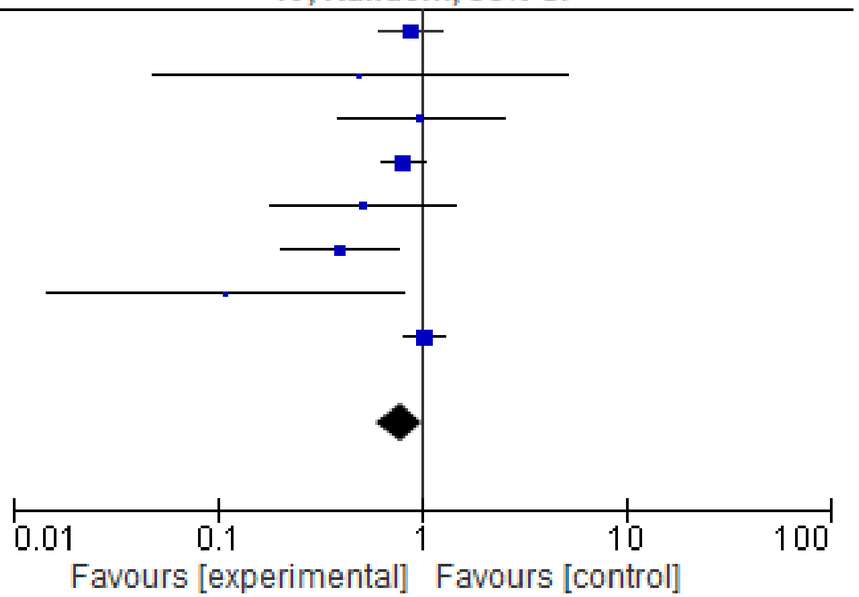


# There was marginal difference in the incidence of Oral Mucositis after chamomile prophylaxis

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Fidler et al 1996 | 33 | 82 | 37 | 82 | 21.1% | 0.89 [0.62, 1.27] | 1996 |
| Renani et al 2011 | 1 | 26 | 2 | 26 | 1.2% | 0.50 [0.05, 5.18] | 2011 |
| Braga et al 2015 | 7 | 70 | 9 | 90 | 6.2% | 1.00 [0.39, 2.55] | 2015 |
| Tavakoli Ardakani et al 2016 | 20 | 27 | 30 | 33 | 26.6% | 0.81 [0.64, 1.04] | 2016 |
| dos Reis et al 2016 | 4 | 20 | 7 | 18 | 5.1% | 0.51 [0.18, 1.47] | 2016 |
| Pourdeghatkarm et al 2017 | 8 | 31 | 20 | 31 | 10.8% | 0.40 [0.21, 0.77] | 2017 |
| AbdElwadoud et al 2019 | 1 | 30 | 7 | 23 | 1.5% | 0.11 [0.01, 0.83] | 2019 |
| Elhadad et al 2020 | 27 | 30 | 13 | 15 | 27.4% | 1.04 [0.82, 1.31] | 2020 |
| **Total (95% CI)** | | **316** | | **318** | **100.0%** | **0.78 [0.61, 1.01]** | |
| Total events | 101 | | 125 | | | | |

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 13.28$, df = 7 (P = 0.07); $I^2 = 47\%$

Test for overall effect: Z = 1.86 (P = 0.06)

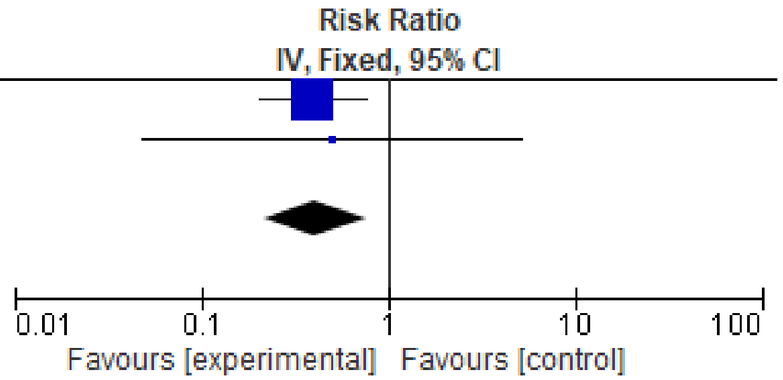


# Chamomile prophylaxis significantly reduced the incidence of OM in pediatric populations

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Pourdeghatkarm et al 2017 | 8 | 31 | 20 | 31 | 92.8% | 0.40 [0.21, 0.77] |
| Renani et al 2011 | 1 | 26 | 2 | 26 | 7.2% | 0.50 [0.05, 5.18] |
| **Total (95% CI)** | | **57** | | **57** | **100.0%** | **0.41 [0.22, 0.76]** |
| Total events | 9 | | 22 | | | |

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%

Test for overall effect: Z = 2.81 (P = 0.005)

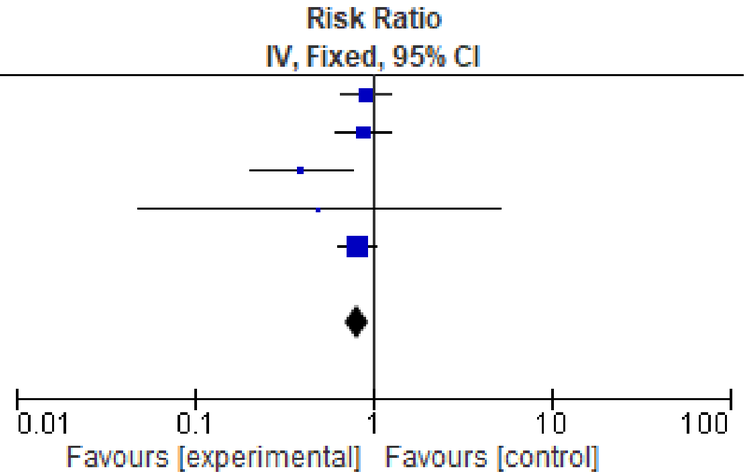



# Chamomile prophylaxis without adjunctive oral care significantly reduced the incidence of OM

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Elhadad et al 2020 | 12 | 15 | 13 | 15 | 26.6% | 0.92 [0.67, 1.27] |
| Fidler et al 1996 | 33 | 82 | 37 | 82 | 21.7% | 0.89 [0.62, 1.27] |
| Pourdeghatkarm et al 2017 | 8 | 31 | 20 | 31 | 6.5% | 0.40 [0.21, 0.77] |
| Renani et al 2011 | 1 | 26 | 2 | 26 | 0.5% | 0.50 [0.05, 5.18] |
| Tavakoli Ardakani et al 2016 | 20 | 27 | 30 | 33 | 44.7% | 0.81 [0.64, 1.04] |
| **Total (95% CI)** | | **181** | | **187** | **100.0%** | **0.82 [0.69, 0.97]** |
| Total events | 74 | | 102 | | | |

Heterogeneity: Chi² = 5.57, df = 4 (P = 0.23); I² = 28%

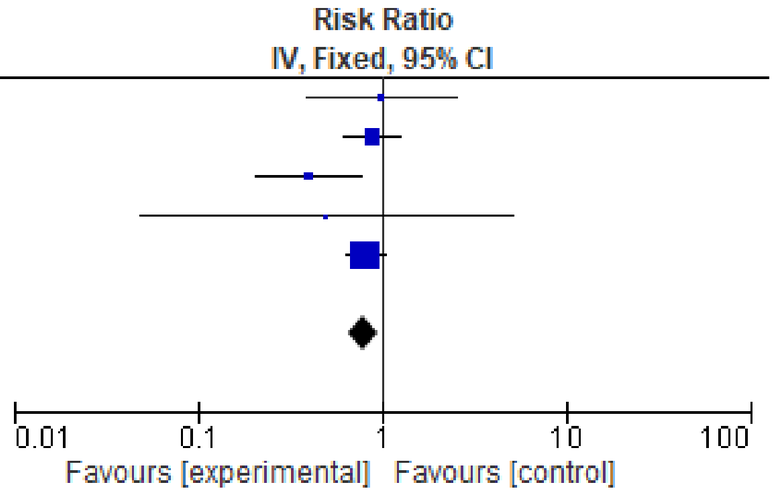
Test for overall effect: Z = 2.37 (P = 0.02)



# Chamomile mouthwash significantly reduced the incidence of Oral Mucositis compared to topical chamomile preparation

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Braga et al 2015 | 7 | 70 | 9 | 90 | 4.1% | 1.00 [0.39, 2.55] |
| Fidler et al 1996 | 33 | 82 | 37 | 82 | 28.4% | 0.89 [0.62, 1.27] |
| Pourdeghatkarm et al 2017 | 8 | 31 | 20 | 31 | 8.5% | 0.40 [0.21, 0.77] |
| Renani et al 2011 | 1 | 26 | 2 | 26 | 0.7% | 0.50 [0.05, 5.18] |
| Tavakoli Ardakani et al 2016 | 20 | 27 | 30 | 33 | 58.4% | 0.81 [0.64, 1.04] |
| **Total (95% CI)** | | **236** | | **262** | **100.0%** | **0.79 [0.65, 0.96]** |
| Total events | 69 | | 98 | | | |

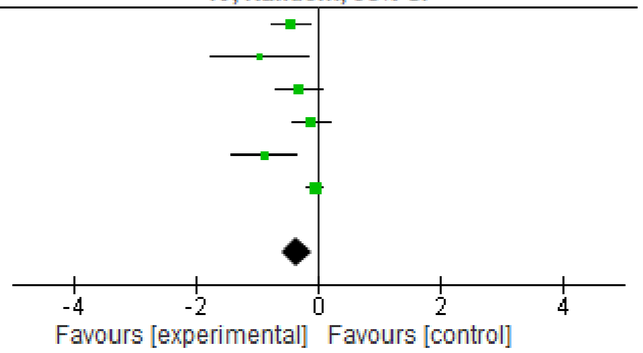
Heterogeneity: Chi² = 5.09, df = 4 (P = 0.28); I² = 21%
Test for overall effect: Z = 2.42 (P = 0.02)




# Chamomile prophylaxis significantly reduced the severity of Oral Mucositis

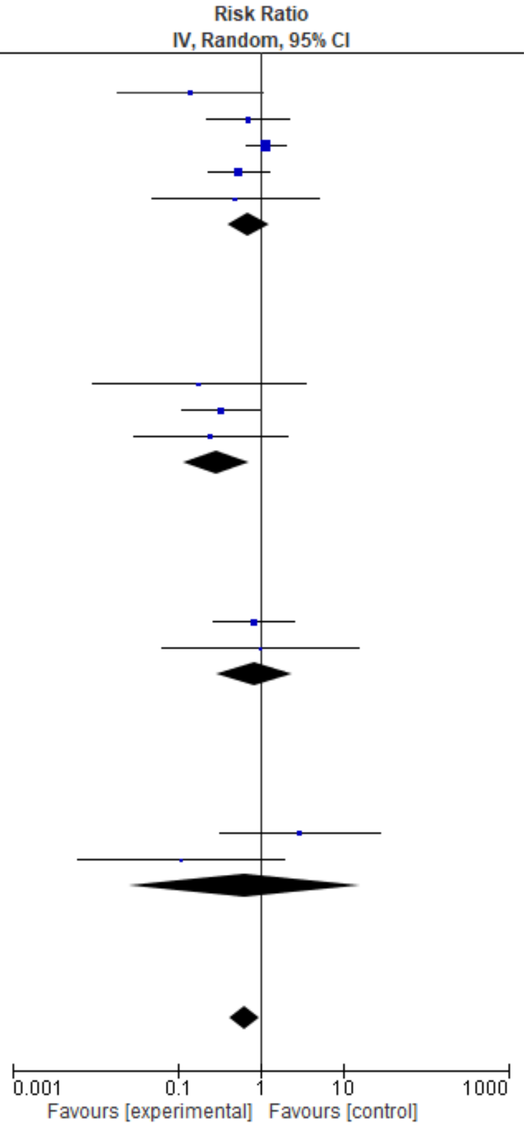
| Study or Subgroup | Experimental Mean | Experimental SD | Experimental Total | Control Mean | Control SD | Control Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| AbdElwadoud et al 2019 | 0.033333 | 0.182574 | 30 | 0.466667 | 0.860366 | 30 | 19.1% | -0.43 [-0.75, -0.12] |
| Braga et al 2015 | 1.15 | 1.21 | 30 | 2.1 | 1.1 | 10 | 7.4% | -0.95 [-1.76, -0.14] |
| dos Reis et al 2016 | 0.2 | 0.410391 | 20 | 0.5 | 0.70710678 | 18 | 17.1% | -0.30 [-0.67, 0.07] |
| Fidler et al 1996 | 0.682927 | 1.064327 | 82 | 0.780488 | 1.030694 | 82 | 18.9% | -0.10 [-0.42, 0.22] |
| Pourdeghatkarm et al 2017 | 0.354839 | 0.709384 | 31 | 1.225806 | 1.334408 | 31 | 12.5% | -0.87 [-1.40, -0.34] |
| Renani et al 2011 | 0.038462 | 0.196116 | 26 | 0.076923 | 0.271746 | 26 | 25.0% | -0.04 [-0.17, 0.09] |
| **Total (95% CI)** | | | **219** | | | **197** | **100.0%** | **-0.34 [-0.60, -0.08]** |

Heterogeneity: Tau² = 0.07; Chi² = 17.53, df = 5 (P = 0.004); I² = 71%
Test for overall effect: Z = 2.59 (P = 0.010)



# Chamomile prophylaxis significantly reduced the incidence of grade 2 Oral Mucositis

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **2.1.1 Grade 1** | | | | | | |
| AbdElwadoud et al 2019 | 1 | 30 | 7 | 30 | 3.9% | 0.14 [0.02, 1.09] |
| dos Reis et al 2016 | 4 | 20 | 5 | 18 | 10.8% | 0.72 [0.23, 2.27] |
| Fidler et al 1996 | 21 | 82 | 18 | 82 | 29.5% | 1.17 [0.67, 2.02] |
| Pourdeghatkarm et al 2017 | 6 | 31 | 11 | 31 | 16.9% | 0.55 [0.23, 1.29] |
| Renani et al 2011 | 1 | 26 | 2 | 26 | 3.0% | 0.50 [0.05, 5.18] |
| **Subtotal (95% CI)** | | **189** | | **187** | **64.2%** | **0.72 [0.41, 1.26]** |
| Total events | 33 | | 43 | | | |
| Heterogeneity: Tau² = 0.11; Chi² = 5.50, df = 4 (P = 0.24); I² = 27% | | | | | | |
| Test for overall effect: Z = 1.14 (P = 0.25) | | | | | | |
| **2.1.2 Grade 2** | | | | | | |
| dos Reis et al 2016 | 0 | 20 | 2 | 18 | 1.9% | 0.18 [0.01, 3.54] |
| Fidler et al 1996 | 4 | 82 | 12 | 82 | 11.8% | 0.33 [0.11, 0.99] |
| Pourdeghatkarm et al 2017 | 1 | 31 | 4 | 31 | 3.6% | 0.25 [0.03, 2.11] |
| **Subtotal (95% CI)** | | **133** | | **131** | **17.3%** | **0.30 [0.12, 0.75]** |
| Total events | 5 | | 18 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 2 (P = 0.92); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.57 (P = 0.01) | | | | | | |
| **2.1.3 Grade 3** | | | | | | |
| Fidler et al 1996 | 5 | 82 | 6 | 82 | 10.9% | 0.83 [0.26, 2.62] |
| Pourdeghatkarm et al 2017 | 1 | 31 | 1 | 31 | 2.3% | 1.00 [0.07, 15.28] |
| **Subtotal (95% CI)** | | **113** | | **113** | **13.1%** | **0.86 [0.30, 2.46]** |
| Total events | 6 | | 7 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.90); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.29 (P = 0.77) | | | | | | |
| **2.1.4 Grade 4** | | | | | | |
| Fidler et al 1996 | 3 | 82 | 1 | 82 | 3.3% | 3.00 [0.32, 28.25] |
| Pourdeghatkarm et al 2017 | 0 | 31 | 4 | 31 | 2.0% | 0.11 [0.01, 1.98] |
| **Subtotal (95% CI)** | | **113** | | **113** | **5.3%** | **0.66 [0.03, 16.44]** |
| Total events | 3 | | 5 | | | |
| Heterogeneity: Tau² = 3.70; Chi² = 3.13, df = 1 (P = 0.08); I² = 68% | | | | | | |
| Test for overall effect: Z = 0.26 (P = 0.80) | | | | | | |
| **Total (95% CI)** | | **548** | | **544** | **100.0%** | **0.65 [0.43, 0.99]** |
| Total events | 47 | | 73 | | | |
| Heterogeneity: Tau² = 0.08; Chi² = 12.86, df = 11 (P = 0.30); I² = 14% | | | | | | |
| Test for overall effect: Z = 2.02 (P = 0.04) | | | | | | |
| Test for subgroup differences: Chi² = 3.07, df = 3 (P = 0.38), I² = 2.2% | | | | | | |



# CONCLUSION

Chamomile Mouthwash may be considered for the following contexts:

- Pediatric population
- Prophylaxis in the absence of other medical palliative options
- Reduction of severity and incidence of Grade 2 Oral mucositis
- Reduction of severity as compared to topical preparations

This study highlights the potential palliative properties of natural products as in Chamomile preparations for reducing morbidities associated with chemotherapy.