

**LEMBAR**  
**HASIL PENILAIAN SEJAWAT SEBIDANG ATAU PEER REVIEW**  
**KARYA ILMIAH : JURNAL ILMIAH**

Judul Jurnal Ilmiah (Artikel) : Citrus sinensis (L) Peels Extract Inhibits Metastasis of Breast Cancer Cells by Targeting the Downregulation Matrix Metalloproteinases-9

Jumlah Penulis : 3 orang (Meiny Suzery, **Bambang Cahyono**, Nur Dina Amalina)

Status Pengusul : penulis ke-2

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- d. Penerbit : Scientific Foundation SPIROSKI
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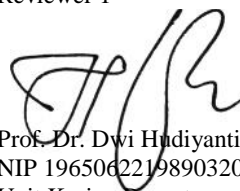
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Prof. Dr. Dwi Hndiyanti, M.Sc  
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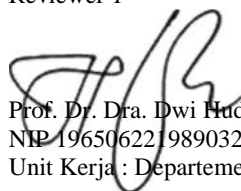
**2. Ruang lingkup dan kedalaman pembahasan:** Artikel ini membahas tentang eksplorasi peran Citrus sinensis (L.) peels extract (CSP) dalam kombinasi dengan DOX untuk menghambat migrasi sel metastatik MDA-MB-231 BC. Eksplorasi dilakukan baik dengan wet experiment maupun in silico dengan molecular docking. Data kombinasi CSP dan DOX hanya in silico, data sitotoksitas hanya untuk masing-masing CSP dan DOX (fig 1 dan fig.2), tidak ada data kombinasi CSP dan DOX. Data dan pembahasan cukup berkontribusi pada pengembangan keilmuan. Namun demikian judul yang diberikan belum secara eksplisit menggambarkan topik dan temuan yang dibahas.

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**2. Ruang lingkup dan kedalaman pembahasan:**

Lingkup artikel ini adalah ekstrak kupasan buah Citrus sinensis (CSP) untuk menghambat metastasis sel kanker Breast (payudara) dengan target downregulasi matriks Metalloproteinases-9. Pembahasan dilakukan dengan melakukan penelitian penurunan sel MDA-MB membandingkan antara CSP dengan DOX (obat kanker yang umum digunakan) serta kombinasi antara keduanya, walaupun beberapa nya tidak apple to apple namun penelitian ini mampu menunjukkan efek sinergi antara CSP-DOX. Penelitian ini juga menggunakan pendekatan komputasi secara Docking dan analisa statistika menggunakan ANOVA. (11,5)

**3. Kecukupan dan kemutakhiran data/informasi dan metodologi:**

Metode yang digunakan cukup memadai yaitu secara laboratorium dan penggunaan software serta komputasi. Reference yang dirujuk cukup banyak lebih dari 50% merupakan reference yang terbit sebelum 5 tahun terbitnya artikel jurnal ini (Juni 2021) dari 24 references. (11,5)

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Semarang, Mei 2022  
Reviewer 2



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# Citrus sinensis (L) peels extract inhibits metastasis of breast cancer cells by targeting the downregulation matrix metalloproteinases-9

Suzery, Meiny<sup>a</sup> ; Cahyono, Bambang<sup>a</sup>; Amalina, Nur Dina<sup>b</sup>

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<sup>a</sup> Department of Chemistry, Faculty of Sciences and Mathematics, Diponegoro University, Semarang, Indonesia<sup>b</sup> Faculty of Mathematics and Natural Sciences, Semarang State University, Semarang, Indonesia[View PDF](#) [Full text options](#) [Export](#)**Abstract**

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**Abstract**

**BACKGROUND:** Long-term use of doxorubicin (DOX) chemotherapy causes several side effects, especially induction of metastasis on breast cancer (BC). There is an urgent need to identify novel agent with low side effect targeting BC metastasis. Citrus sinensis (L.) peels extract (CSP) has long been used for the treatment of several cancers. However, its anti-metastatic potential against BC metastatic remains unclear. **AIM:** This study aimed to explore the role of CSP in combination with DOX in

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Mursiti, S. , Amalina, N.D. , Marianti, A.  
(2021) *Journal of Physics: Conference Series*

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### **Citrus sinensis (L) Peels Extract Inhibits Metastasis of Breast Cancer Cells by Targeting the Downregulation Matrix Metalloproteinases-9**

Meiny Suzery, Bambang Cahyono, Nur Dina Amalina (Author)

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PDF



## Citrus sinensis (L) Peels Extract Inhibits Metastasis of Breast Cancer Cells by Targeting the Downregulation Matrix Metalloproteinases-9

Meiny Suzery<sup>1\*</sup>, Bambang Cahyono<sup>1</sup>, Nur Dina Amalina<sup>2</sup>

<sup>1</sup>Department of Chemistry, Faculty of Sciences and Mathematics, Diponegoro University, Semarang, Indonesia; <sup>2</sup>Pharmacy Study Program, Faculty of Mathematics and Natural Sciences, Semarang State University, Semarang, Indonesia

### Abstract

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**Citation:** Suzery M, Cahyono B, Amalina ND. *Citrus sinensis* (L) Peels Extract Inhibits Metastasis of Breast Cancer Cells by Targeting the Downregulation Matrix Metalloproteinases-9. Open Access Maced J Med Sci. 2021 Jun 27; 9(B):464-469. https://doi.org/10.3889/oamjms.2021.6072  
**Keywords:** *Citrus sinensis*; Co-chemotherapy; Matrix metalloproteinases-9; Metastasis; MDA-MB-231 breast cancer cells

**\*Correspondence:** Meiny Suzery, Department of Chemistry, Faculty of Sciences and Mathematics, Diponegoro University, Semarang, Indonesia.  
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**Competing Interests:** The authors have declared that no competing interests exist

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**BACKGROUND:** Long-term use of doxorubicin (DOX) chemotherapy causes several side effects, especially induction of metastasis on breast cancer (BC). There is an urgent need to identify novel agent with low side effect targeting BC metastasis. *Citrus sinensis* (L.) peels extract (CSP) has long been used for the treatment of several cancers. However, its anti-metastatic potential against BC metastatic remains unclear.

**AIM:** This study aimed to explore the role of CSP in combination with DOX in inhibiting the migration of metastatic BC MDA-MB-231 cells.

**MATERIALS AND METHODS:** Potential cytotoxic in single and combination was analyzed 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay [MTT] assay). The anti-metastatic activities of several major compounds on CSP including hesperetin, tangeretin, nobiletin, naringenin, and hesperidin were screened by molecular docking under protein-ligand ant system software.

**RESULTS:** Based on molecular docking, we revealed that the selected protein target matrix metalloproteinases-9 (PBD ID:2OVX) has lower docking score for hesperetin, tangeretin, nobiletin, naringenin, and hesperidin compare to DOX. CSP and DOX individually exhibited strong cytotoxic effect on MDA-MB-231 cells under MTT assay with IC50 value of 344 µg/mL and 85 nM, respectively. Furthermore, CSP in combination with DOX synergistically increased the cytotoxicity of DOX. Here, we showed that CSP can specifically suppress the side effect of DOX-induced metastasis by reduces doses of DOX. However, low doses of DOX in combination with CSP still potential inhibited cancer cells growth.

**CONCLUSION:** CSP increased the cytotoxicity and inhibited the induction of metastasis by DOX in BC cells so that CSP potential to be developed as co-chemotherapeutic agent.

### Introduction

Breast cancer (BC) is the most frequent cancer among women, with 3.8 million death case in 2019 [1]. The most cases of BC death are mainly due to metastasis of primary cancer to various organ sites. It is a multi-faceted mechanism that results from orchestrated activities, including adhesion, invasion, and migration [2]. Extracellular matrix degradation (ECM) by proteolytic enzymes and subsequent cancer invasion is important early stages of metastasis [3]. Matrix metalloproteinases (MMPs) is the most crucial proteolytic enzyme that degrades the ECM. Accordingly, the MMP-9 expression is associated with BC metastatic and invasion [4], [5]. Therefore, it is necessary to develop new strategy that has the potential to inhibit metastatic BC cells.

Recently, the main treatment for BC metastatic is chemotherapy [6]. However, this therapy is not effective and often leads to side effect such as metastatic and relapse [7]. The

previous study reported that doxorubicin (DOX) induces lamellipodia, this formation is the initial stage of metastatic [8], [9]. Thus, studies toward finding efficient therapeutic strategies with minimum side effects are critical for expansion of existing treatment options for BC. Natural herbal medicine is rich sources of bioactive molecules and being developed to compensate for the drawbacks and toxicity of chemotherapy. Flavonoid from *Citrus sinensis* proven to have an anticancer activity with multiple target side on several type of cancer. Hesperetin, a secondary metabolite of *C. sinensis* inhibited Rac-1 expression, the expression of a gene that regulated metastatic [10]. Hesperidin is also shown to be inhibited MCF-7 cancer cell grow [11]. However, the mechanism of *C. sinensis* for inhibiting DOX-induced metastasis is remain unclear. In this study, we investigated the effect of *C. sinensis* peels extract (CSP) in combination with DOX on BC metastatic MDA-MB-231 proliferation and its molecular mechanisms of action through *in silico* approach.



# Anorectal Manometry on Children: A Moroccan Series and Literature Review

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## Abstract

**BACKGROUND:** Anorectal manometry (ARM) is a test used to evaluate the rectum and anus functions. It also helps to diagnose several conditions such as fecal incontinence and constipation. This test is being increasingly performed on children of all ages.

**AIM:** The aim of our study is to determine the benefit of ARM on children and to report our experience.

**METHODS:** Over a period of 4 years, data and test results of 273 children were analyzed.

**RESULTS:** Out of 273 patients (68.5% boys and 31.5% girls with a mean age of 9 years), 154 patients (51.6%) had fecal incontinence (Group 1), 75 children (27.5%) had chronic constipation (CC) (Group 2), and 37 children (13.6%) had both of them (Group 3). An awake manometry was performed on 248 children (91%); however, under sedation, the test allowed us the exclusion of Hirschsprung's disease (HD) in 21 children (84%). Bad anal contraction was present in 25% of patients in group 1 and 21.6% of patients in group 3. The statistical analysis showed a significant difference in age ( $p = 0.022$ ) and resting pressure ( $p = 0.050$ ) between the three groups. Children with fecal incontinence had a higher rate of dyssynergy, 80.2% and 83.8%, in groups 1 and 3, respectively, compared to 60.4% in patients with CC ( $p = 0.852$ ).

**CONCLUSION:** ARM is the gold standard for terminal constipation and encopresis exploration on children. In our study, this test was efficient for the exclusion of HD in infants suffering from constipation, in the other hand, we found a high rate of dyssynergy on children with fecal incontinence (80%) and a biofeedback therapy was proposed in this case.

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## Introduction

Anorectal manometry (ARM) is a diagnostic test used to evaluate the rectum and anus functions. For more than a century, it was the exploration of choice for adults suffering from chronic constipation (CC) resistant to conservative treatments (diet, laxatives, toileting regime), and for defecation disorders diagnosis including evacuation difficulties (dyssynergic defecation) and fecal incontinence (FI) [1], it was also used to study anorectal function before or after bowel surgery.

On children presenting the same symptoms, ARM was not commonly used as part of routine investigations.

Finally, this test is increasingly used on children of all ages, particularly for the screening of Hirschsprung's disease (HD), the most important indication for ARM in pediatric population. This test can be performed awake, under general anesthesia (GA), or under sedation.

Little data are available on ARM on children in the literature, the knowledge of normal values is very

limited even for the protocol used. More studies are needed for better comprehension and standardization of data on children.

In Morocco, our unit was the first to perform ARM on children. The objective of this study was to determine the benefit of ARM on children, the modalities, stages, and especially it is particularities on this population, as well as to report a Moroccan experience. To the best of our knowledge, this study is the first in our country to prove the benefit of ARM on children.


## Methods

A retrospective, observational, and analytic study was conducted over a period of 4 years. All children referred for ARM to the EFD-Hepatogastroenterology unit, Ibn Sina Hospital, Rabat, Morocco, were included in the study.

An informed consent/assent of the parents and underage children was obtained before the procedure.



## Mesenteric Vessel Thrombosis Treatment Experience

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### Abstract

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**BACKGROUND:** One of the most serious diseases among all emergency abdominal pathology is an acute violation of the mesenteric blood circulation. The rapid development of intestinal ischemia results in its infarction and necrosis.

**AIM:** The study aims to assess the survival rate of patients with mesenteric vascular thrombosis, taking into account, the predictor characteristics influence of disease development factors.

**METHODS:** The study presents a retrospective analysis of mesenteric vascular thrombosis clinical cases for 2016–2019. During this period, there were 147 patients with an established diagnosis at the Irkutsk Clinical Hospital No. 1, 21 of them met the study criteria.

**RESULTS:** According to the type of thrombosis, there were two groups – occlusive (Group I, n = 11) and non occlusive (Group II, n = 10). Four patients (36.3%) of Group I and 7 patients (70%) of Group II (p = 0.388) recovered from the disease. Three patients (27.2%) of Group I and 4 patients (40%) of Group II (p = 0.662) received conservative therapy, 2 of them (66.6%) in Group I and 4 (100%) in Group II (p = 0.724) recovered from the disease. In addition, the authors performed a mortality assessment, according to the timing of the visit to a medical institution. Four (50%) out of eight patients who applied in the first 12 h, 2 (66%) out of three – in the first 12–24 h, and 5 (50%) out of 10 for more than 24 h of illness had a positive treatment result in the combined group.

**CONCLUSION:** The patients over 70 years old with peritoneal symptoms and established intestinal necrosis have an extremely unfavorable prognosis. The primary mesenteric vessel thrombosis with additional contrast angiography still gives a moderate treatment prognosis.

## Introduction

One of the most serious diseases among all emergency abdominal pathologies is an acute violation of the mesenteric blood circulation. The rapid development of intestinal ischemia leads to its infarction and necrosis [1]. According to Russian clinical guidelines, acute mesenteric ischemia (AMI) manifests in a partial or complete cessation of arterial or venous blood flow within the mesenteric circulation [2].

The number of patients with this pathology increases annually because of the growing number of elderly and senile people, as well as cardiovascular pathology [1], [3]. Acute violation of mesenteric circulation varies from 0.09% to 0.2% in the structure of all urgent abdominal pathology [3]. The average age of patients with this pathology is around 70 years old [4]. There are no gender differences in the incidence of the disease [1]. According to additional studies, most often the disease affects the superior mesenteric artery (up to 90%) [5].

In surgical practice, there are occlusive and non-occlusive forms of mesenteric vascular lesions. Occlusive forms include mesenteric artery embolism

AMI (up to 50% of cases), mesenteric artery thrombotic AMI (15–25%), and mesenteric vein thrombotic AMI (5–15%). Non-occlusive mesenteric ischemia is relatively rare (5–20%) [6].

The disease manifests in various and non-specific ways, a latent course complicates the diagnosis verification [3]. Irreversible changes occur quickly especially in the case of occlusion, which gives a terribly poor prognosis for life and recovery [7]. The most reliable diagnostic techniques are various mesenteric vessels examining, such as angiography, allowing in some cases at the same time remove a thrombus [3]. The main treatment goal is to restore vascular patency or remove non-viable intestinal segments and correct complications [3]. The study aims to compare the results of mesenteric vascular thrombosis treatment.

## Methods

The local ethical committees of the Federal State Budgetary Educational Institution of Higher