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Research Article
PDGF-β and IL-18 Expressions on Carcinoma Cervical by *Rhodomyrtus tomentosa*

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Abstract
Background and Objective: Cervical cancer, along with lung and breast cancer, is one of Indonesia's most aggressive gynaecological diseases. *Rhodomyrtus tomentosa* has antioxidant and antiproliferative properties that could be developed into herbal medicines for molecular therapy. The IL-18 and PDGF-β are tumour-promoting agent proteins that may be therapeutic targets for a variety of cancers that were investigated in this study. **Materials and Methods:** Rats were classified into five groups: Group C- is the control group, Group C+ is the cancer model group and Group RHO200 is the *Rhodomyrtus tomentosa* 100 mg^{-1} b.wt., rat group, Group RHO400 is the *Rhodomyrtus tomentosa* 200 mg^{-1} b.wt., rat group and Group RHO400 is the *Rhodomyrtus tomentosa* 400 mg^{-1} b.wt., rat group. The rats were dissected 30 days after receiving *Rhodomyrtus tomentosa*. Immunohistochemistry is used to stain cervical tissues. **Results:** The expression of IL-18 and PDGF-β was significantly different ($p<0.01$). The IL-18 and PDGF-β were most abundant at the lowest *Rhodomyrtus tomentosa* doses (100-200 mg kg^{-1} b.wt.), while they were least abundant at the 400 mg kg^{-1} b.wt., doses. Histological analysis revealed that the highest dose of IL-18 and PDGF-β expression reduced abnormal tissue and the space between tumours, followed by several carcinoma cells that stopped growing. **Conclusion:** *Rhodomyrtus tomentosa* can be used as a herbal therapy to reduce the expression of PDGF-β and IL-18 (two cancer marker agents).

Key words: Cervical cancer, IL-18, immunohistochemistry, molecular therapy, PDGF-β, *Rhodomyrtus tomentosa*, lipid peroxidation

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Cervical cancer is one of the most severe gynaecological illnesses because of the quick development of functioning tumour vascular tissue[1]. Cervical cancer has a high incidence and mortality rate. In Indonesia, national cervical cancer screening coverage remains low at 12%, emphasizing the need to investigate screening facilitators and barriers[2]. In Indonesia, where lung cancer, breast cancer and cervical cancer are the three main causes of cancer-related fatalities, the International Agency for Research on Cancer (IARC) described 348.809 cancer cases and 207.210 cancer deaths in their 2018 report[2].

Rhodomyrtus tomentosa is a Myrtaceae-family herbal plant that grows in the yards of Indonesians[3]. *Rhodomyrtus tomentosa* has antioxidant and antiproliferative properties. Flavones, 6 triterpenes, 7-9 steroids, 7 hydrolyzed tannins, 10 and acylphloroglucinols have been reported as chemical constituents of *Rhodomyrtus tomentosa*[3]. An examination of the pharmacological activity of *Rhodomyrtus tomentosa* revealed that this edible medicinal herb has antibacterial, antitumor, anti-inflammatory and antioxidant properties both *in vivo* and *in vitro*[3]. This herb can reduce lipid peroxidation, increase HSP-70 expression, improve free radical scavenging capacity and improve the histology of placenta and diabetic wounds[4-8]. It has a high antioxidant capacity and is a potential source of health-promoting substances due to its high phenolic content[9].

Tumour angiogenesis is critical in the progression of tumour growth, invasion and metastasis[10]. Through autocrine and/or paracrine mechanisms, Platelet-Derived Growth Factor β (PDGF-β) promotes tumour angiogenesis and invasion[10]. PDGF-β specifically binds to the PDGFR receptor in pancreatic cancer cell lines, activating the Notch-1 and NF-kB signalling pathways[11]. The PDGF-β has been shown to raise interstitial fluid pressure (IFP), which is thought to suppress intratumoral blood vessels and thus affect vascular function. In gastric carcinoma, PDGF-β plays an important role in angiogenesis[11]. PDGF-β is a tumour-promoting factor and a potential therapeutic target for a variety of human carcinomas, including breast cancer[12]. However, little is understood about the function of PDGF family members in the growth of healthy breast tissue, the development of breast cancer and the dynamics of the tumour microenvironment[12]. It has been demonstrated that PDGF signalling has a role in solid tumour angiogenesis, tumour stromal recruitment and autocrine encouragement of tumour cell proliferation[13]. The PDGF-β inhibition reduces cervical cancer cell invasion. Interstitial fluid pressure rises as a result of PDGF signaling[12,13]. Inhibiting PDGF signalling has been shown in several studies to have anti-angiogenic and anti-tumour effects, suggesting that it may increase the effectiveness of chemotherapy[14].

Interleukin-18 (IL-18) is an immune-stimulating cytokine with antitumor activity[15]. The IL-18 is a potential option for lymphoma or lymphoid leukaemia gene therapy since it is crucial in tying the inflammatory immune response to tumour formation[15]. A non-invasive marker called IL-18 is suspected to aid in metastasis. Serum IL-18 may serve as a helpful biological prognostic indicator on its own[16]. The IL-18 gene polymorphism is a significant genetic risk factor for cervical neoplasms[17]. The IL-18 is a proinflammatory and immune-regulatory cytokine[15]. Casp1 enzymatically processes the inactive precursor (pro-IL-18) into the mature form of IL-18[17]. Through the stimulation of NK and/or T cell responses, IL-18 has been studied in clinical trials on cancer patients and has demonstrated anti-tumour effectiveness in numerous preclinical models of cancer immunotherapy[18,19].

The findings of the study on PDGF-β and IL-18 expressions increase the herb's potential as a treatment for cancer in molecular therapy and offer solid justification for its prospective therapeutic application in contemporary medicine. Before using human cells, it was decided to find out and examine how *Rhodomyrtus tomentosa* affected the expression of PDGF-β and IL-18 in the cervical histopathology of rats. *Rhodomyrtus tomentosa* was reduced in size to a micro colloidal state to improve cell penetration and bioavailability. It is envisaged that this plant will be used to create medications for molecular cancer therapy in people.

MATERIALS AND METHODS

Materials: *Rhodomyrtus tomentosa* was discovered in Labuhanbatu, Indonesia's North Sumatera Province. Distilled benzopyrene (50 mg) in corn oil (MFCD00003602, Merck, Vietnam Ltd.,). Anti-PDGF-β antibody (Abcam, Cambridge, UK, Catalogue A Number: ab23914, Rabbit polyclonal to PDGF). Mouse monoclonal antibody against the receptor for interleukin-18 (Catalog number: 14028. Merck Life Science BV, Hoeilaart Belgium).

Preparation of *Rhodomyrtus tomentosa*: The ethanol extract of *Rhodomyrtus tomentosa* was created through maceration with a 96% technical ethanol solvent. Five hundred grams of *Rhodomyrtus tomentosa* dry powder were macerated with technical ethanol (96%) and tightly closed for 24 hrs at room temperature. A Buchner funnel and a vacuum pump were used to filter the maceration results. The filtered residue was macerated twice more using the same method. The sappanwood ethanol extract was concentrated with a rotary evaporator and dried for 8 hrs in a freeze-dryer to produce a solid ethanol extract. For sonification, 0.5 mg of *Rhodomyrtus tomentosa* extract was added to the Tween 20 solution. Before adding capriol 90 and homogenizing, PEG 400 was added and sonicated. The prepared substance is dissolved in distilled water (1:100), homogeneously mixed with an ultrasonic device and the particle size of the clear solution is calculated.

Experimental animals: The study was conducted in the Biology Laboratory, Pathology Laboratory and Anatomy Laboratory of the Faculty of Medicine at the University of Sumatera Utara from January to August, 2022. For 30 days, the medication is administered to five rat groups: *Rhodomyrtus tomentosa* 100 mg^{-1} b.wt., group, *Rhodomyrtus tomentosa* 200 mg^{-1} b.wt., group, *Rhodomyrtus tomentosa* 400 mg^{-1} b.wt., group, Group C- is the control group, Group C+ is the cancer model group and Group RHO100 is the *Rhodomyrtus tomentosa* 100 mg^{-1} b.wt., group. The rats are dissected 30 days after receiving *Rhodomyrtus tomentosa*. To stain the cervical tissues, immunohistochemistry is performed. The USU Faculty of Mathematics and Natural Sciences Ethics Committee for Handling Experimental Animals has approved this study (Ethical Clearance: No. 043/KEPH-FMIPA/2022).

Rats model of cervical cancer: The 36 rats (*Rattus norvegicus*) weighing 180-200 g were donated for this study by the Animal House Laboratory at the University of Sumatera Utara. The rats are fed standardized rat pellets and provided ample water each day before the trial and they spend four weeks getting used to the lab environment. By injecting benzopyrene 50 mg^{-1} b.wt., into the cervix and letting the tumour develop for 3 months, the rats were used as animal models for cancer.

Making paraffin blocks: The cervical is taken out of storage after being fixed in formalin and immersed in xylol for 15 min. The tissues were rinsed with distilled water after 5 min of alternating immersion in 96 and 70% pure alcohol. The tissues were subjected to hematoxylin dye for 5 min and then rinsed for 3 min in distilled water. For one minute, eosin dye was applied. Before submerging in xylol, the slides were dried in 70, 96 and 100% alcohol. Light microscope observations were then done[20].

Immunohistochemistry: Slices of the cervix that were 5 m thick and embedded in paraffin were deparaffinized and the endogenous peroxidase activity was reduced for 30 min by treatment with 1% H_2O_2 in methanol. After that, the slides were washed with 0.01 M Tris-buffered saline (TBS pH 7.4). Tissue slices were incubated with Antigen Affinity-purified Polyclonal Antibody, PDGF-β and IL-18, the antibody utilized in this experiment, for a whole night at 4°C. Additionally, Mayer's hematoxylin-neutralized immunoreactivity was discovered by the Vectastain Elite ABC kit from Vector Laboratories in the US[21].

Data analysis: The data was collected and the Kruskal-Wallis and Mann-Whitney Tests were used to analyze categorical data (ordinal) or numerical data that were not normally distributed.

RESULTS

Effect of *Rhodomyrtus tomentosa* on cervical organ weight: The weight of normal and cancerous rat cervixes was compared in Table 1 and demonstrated a significant difference ($p<0.01$) in cervical weight in rat cancer model mice. Additionally, there were significant differences at doses of 100 ($p<0.05$), 200 ($p<0.01$) and 400 mg kg^{-1} b.wt., ($p<0.01$) when administered after cervical injection of benzopyrene 50 mg^{-1} b.wt. Rats' cervical weight significantly changed after receiving *Rhodomyrtus tomentosa* as a treatment.

Analysis of PDG-β expression in carcinoma cervical by *Rhodomyrtus tomentosa*: According to Table 2, there was a significant difference in the expression of PDGF in cervical cancer, with a p-value of 0.00. Compared to the C+ group, the lowest dose of *Rhodomyrtus tomentosa* (100 mg kg^{-1} b.wt.) and the dose of 200 mg kg^{-1} b.wt., both showed a significant difference (average value: $p<0.05$), however, at a dose of 400 mg kg^{-1} b.wt., the significance value dropped to $p<0.01$.

Table 1: Cervical weight after given *Rhodomyrtus tomentosa*

Treatments	Cervical weight (g)
C-	0.29±0.02
C+	1.25±0.07$^{##}$
RHO100	0.96±0.02*
RHO 200	0.43±0.04**
RHO 400	0.39±0.03**

C-: Control, C+: Cervical cancer, RHO100: Cervical cancer +100 mg^{-1} b.wt., of *Rhodomyrtus tomentosa*, RHO200: Cervical cancer+200 mg^{-1} b.wt., of *Rhodomyrtus tomentosa*, RHO400: Cervical cancer+400 mg^{-1} b.wt., of *Rhodomyrtus tomentosa* ($^{##}p<0.01$ vs C-, $^{*}p<0.05$ vs C+ and $^{**}p<0.01$ vs C+)

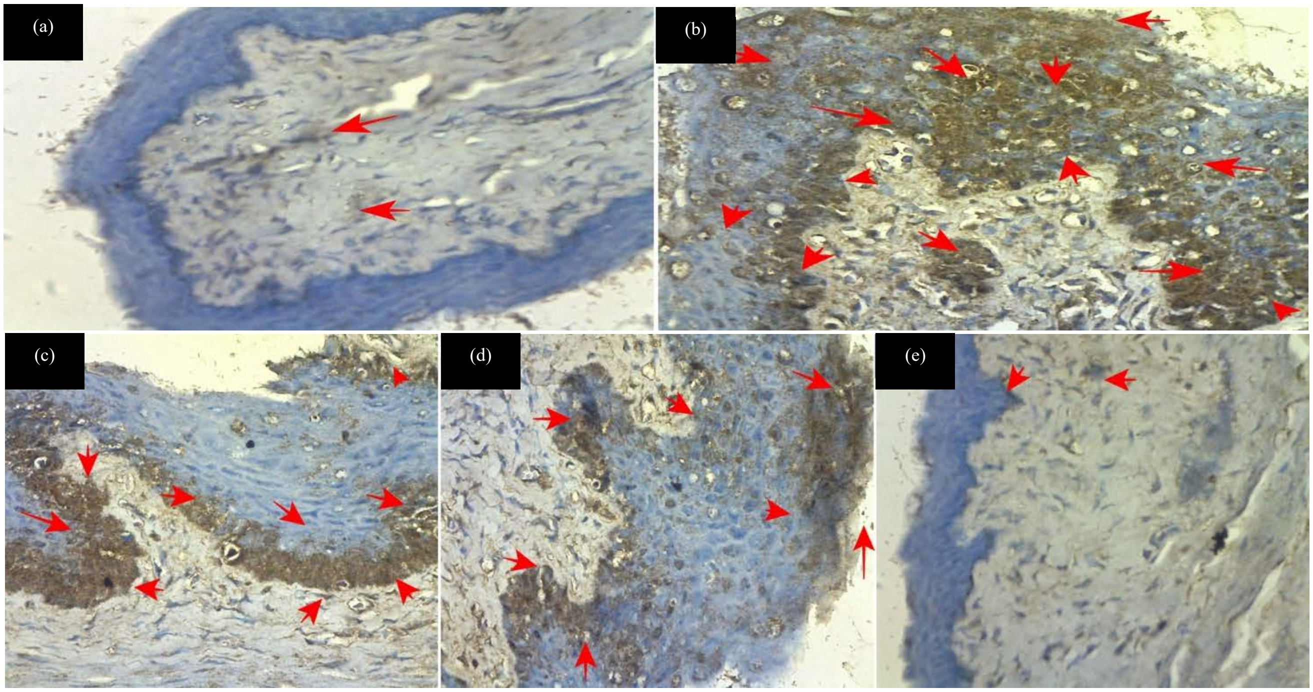

Fig. 1(a-e): PDGF-β expression in carcinoma cervical by *Rhodomyrtus tomentosa*

C-: Control, C+: Cervical cancer, RHO100: Cervical cancer +100 mg^{-1} b.wt., of *Rhodomyrtus tomentosa*, RHO200: Cervical cancer +200 mg^{-1} b.wt., of *Rhodomyrtus tomentosa*, RHO400: Cervical cancer +400 mg^{-1} b.wt., of *Rhodomyrtus tomentosa* and Red arrows: PDGF-β expression (40X)

According to the histological investigation, the cells in Fig. 1a depicting cervical cancer have a typical nuclear structure. Contrarily, the carcinoma progresses by penetration into the stroma and to the basement membrane of the epithelium linked to the cervical cancer lesion in undifferentiated cells restricted to the bottom layer of the epithelium (Fig. 1b). *Rhodomyrtus tomentosa* was administered at a dose of 100 mg kg^{-1} b.wt. and while this reduced nuclear damage compared to the C+ group, the tumour nonetheless advanced due to stromal and basement membrane invasion (Fig. 1c). Following the administration of *Rhodomyrtus tomentosa* 200 mg kg^{-1} b.wt., the histology of cervical cancer started to improve which reduced invasion and intraepithelial neoplasia in the cervical region (Fig. 1d). The tissue shape began to approximate that of the control group (C-) with normal nuclei at the highest dose of 400 mg kg^{-1} b.wt. and the structure of the cell shape and layers started to become regular (Fig. 1e). The untreated group of malignancies' formerly uncontrollable carcinomas have now slowed down and stopped growing into the epithelium. *Rhodomyrtus tomentosa* administration, particularly at a dose of 400 mg kg^{-1} b.wt., can inhibit PDGF expression in cervical carcinoma's histological alterations.

Analysis of IL-18 expression in carcinoma cervical by *Rhodomyrtus tomentosa*: The expression of IL-18 in cervical cancer differs significantly with a p-value of 0.00, according to Table 3. The lowest dose of *Rhodomyrtus tomentosa* (100 mg kg^{-1} b.wt.,) did not significantly differ from the C+ group based on the average value ($p>0.05$). There was a significant difference in the administration of *Rhodomyrtus tomentosa* at doses of 200 and 400 mg kg^{-1} b.wt., ($p<0.05$ and $p<0.01$).

Histological analysis of the Control group (C-) revealed that the cervical tissue was still in normal shape (Fig. 2a). In group C+, a histological investigation showed that the carcinoma had infiltrated the pelvic wall and spread to the cervical tissue and that there was no visible distinction between the pelvic wall cells (Fig. 2b). *Rhodomyrtus tomentosa* was administered at a dose of 100 mg kg^{-1} b.wt. and it still displayed the same histology as the C+ group while outperforming the control group (Fig. 2c). When *Rhodomyrtus tomentosa* was administered at a dose of 200 mg kg^{-1} b.wt., IL-18 expression began to decline, tumour margins were narrowed and certain carcinoma cells ceased proliferating (Fig. 2d). *Rhodomyrtus tomentosa* 400 mg kg^{-1} b.wt., was supplied and the animals almost exactly resembled the

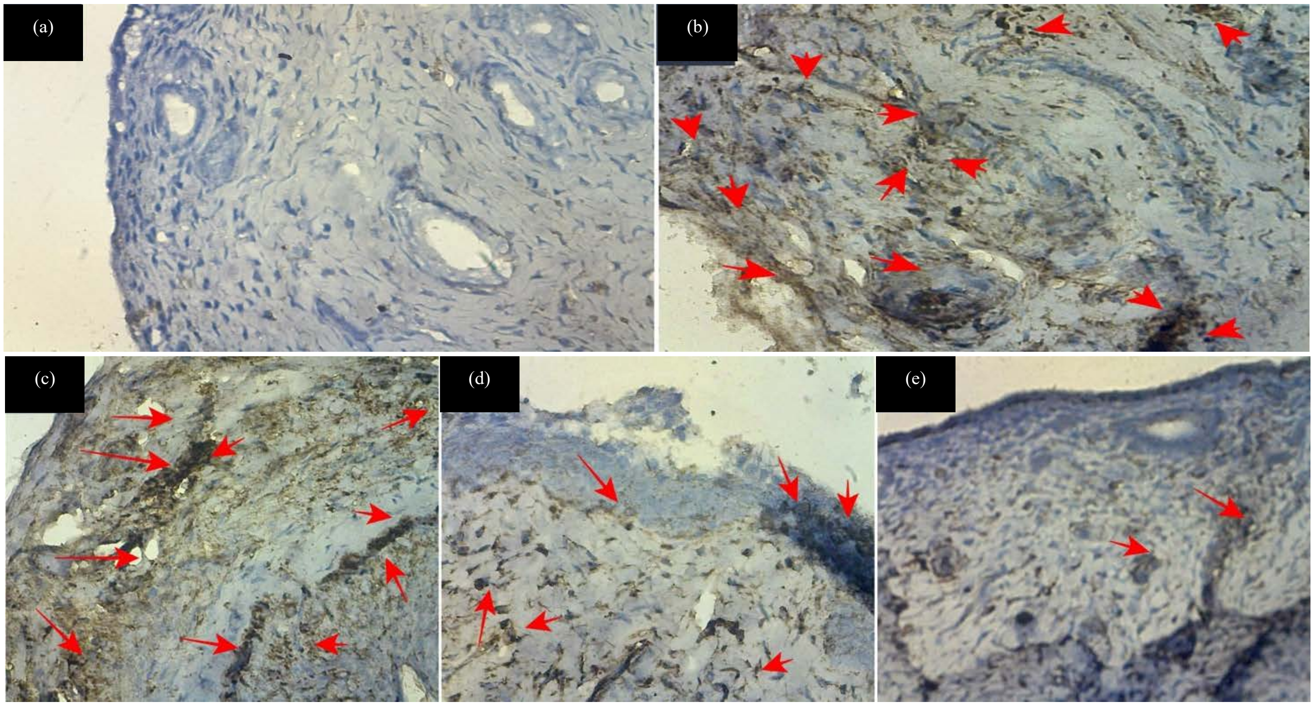

Fig. 2(a-e): IL-18 expression in carcinoma cervical by *Rhodomyrtus tomentosa*
C-: Control, C+: Cervical cancer, RHO100: Cervical cancer +100 mg^{-1} b.wt., of *Rhodomyrtus tomentosa*, RHO200: Cervical cancer +200 mg^{-1} b.wt., of *Rhodomyrtus tomentosa*, RHO400: Cervical cancer +400 mg^{-1} b.wt., of *Rhodomyrtus tomentosa* and Red arrows: IL-18 expression (40X)

Table 2: Analysis of PDGF-β expression in carcinoma cervical

			Mann-Whitney				
Groups	Mean±SD	Kruskal-Wallis	C-	C+	RHO 100	RHO 200	RHO 400
C-	14.93±1.02	0.000		0.001	0.010	0.050	0.060
C+	59.21±8.82$^{\#\#}$				0.040	0.040	0.010
RHO100	30.21±5.88*					0.060	0.040
RHO 200	28.89±5.94*						0.050
RHO 400	18.87±5.12**						

C-: Control, C+: Cervical cancer, RHO100: Cervical cancer+100 mg^{-1} b.wt., of *Rhodomyrtus tomentosa*, RHO200: Cervical cancer+200 mg^{-1} b.wt., of *Rhodomyrtus tomentosa*, RHO400: Cervical cancer+400 mg^{-1} b.wt., of *Rhodomyrtus tomentosa* ($^{\#\#}$p<0.01 vs C-, *p<0.05 vs C+ and **p<0.01 vs C+)

Table 3: Analysis of IL-18 expression in carcinoma cervical

			Mann-Whitney (p-value)				
Groups	Mean±SD	Kruskal-Wallis	C-	C+	RHO 100	RHO 200	RHO 400
C-	8.93±4.71	0.000		0.001	0.001	0.010	0.050
C+	64.52±7.05$^{\#\#}$				0.080	0.050	0.040
RHO100	63.02±5.12^{ns}					0.040	0.010
RHO 200	40.81±5.44*						0.030
RHO 400	19.07±4.55**						

C-: Control, C+: Cervical cancer, RHO100: Cervical cancer+100 mg^{-1} b.wt., of *Rhodomyrtus tomentosa*, RHO200: Cervical cancer+200 mg^{-1} b.wt., of *Rhodomyrtus tomentosa*, RHO400: Cervical cancer +400 mg^{-1} b.wt., of *Rhodomyrtus tomentosa* ($^{\#\#}$p<0.01 vs C-, *p<0.05 vs C+, **p<0.01 vs C+ and ^{ns}p>0.05 vs C+)

control group in terms of appearance. The nucleus began to take on a normal form and aberrant cells, empty spaces and various lesions were minimized (Fig. 2e). *Rhodomyrtus tomentosa*, especially when administered at a dose of 400 mg kg^{-1} b.wt., can decrease the expression of IL-18 in cervical carcinoma's histological changes.

DISCUSSION

The histological abnormalities of cervical cancer can be inhibited by the administration of *Rhodomyrtus tomentosa*, especially at a dose of 400 mg kg^{-1} b. wt. Untreated tumours that had previously expanded freely have now slowed down and stopped producing aberrant cells. Little smooth muscle may be found in the deeper middle layer of the cervix, which is primarily made up of dense connective tissue. Numerous lymphocytes and other leukocytes enter this stroma and pass through the stratified epithelium to bolster the local immune system's ability to combat pathogens[22]. The histopathology of cervical cancer rat tissue demonstrated the participation of *Rhodomyrtus tomentosa* in this case. Antioxidants and cancer were strongly associated since antioxidants are now a popular therapeutic approach. The bulk of chemotherapy and radiation therapy eliminate tumour cells by procedures that do not include antioxidant augmentation, causing irreversible tissue damage[23]. Successful cancer treatment can be achieved by utilizing the proper antioxidant inhibitors and/or free radical-producing agents. In addition to aryl phloroglucinol, flavonoids, tannins and triterpenes, this plant extract has numerous advantages for cell repair[24-26].

The molecular and cellular effects of PDGF inhibition in cervical cells were examined using microarray technology, which revealed changes in gene expression brought on by PDGF silence[27]. Among the biological functions of PDGF are cell movement, cellular growth and proliferation, cardiovascular system development and cell death and survival[11,12]. The PDGF-β silencing does not affect a cell's capacity to proliferate or cause cell death, according to cellular studies on proliferation, apoptosis and invasion[12,13]. This finding implies that additional signalling pathways are activated to keep cell growth and apoptosis under check. Silencing of PDGF reduces cervical cancer cell invasion. It has been demonstrated that antioxidants help lessen the hazardous side effects of cancer treatment[25]. Antioxidant-containing plants, such as *Rhodomyrtus tomentosa*, have been linked to effective cancer treatment with low side effects, which is the basis for the antioxidant intervention[25,26].

The nucleus started to take on a normal form after *Rhodomyrtus tomentosa* was administered at a dose of 400 mg kg^{-1} b.wt., aberrant cells, space and many lesions were reduced and they nearly resembled the control group, showing that the dose could suppress IL-18 expression. Pro-inflammatory cytokine IL-18 is regulated by the secreted protein IL-18 binding protein (IL-18 bp), which can neutralize IL-18[28,29]. Renal function and IFN gamma stimulate IL-18 bp levels in the blood. The IL-18 plays a significant role in the regulation of immune responses and inflammation and it also plays a role in the pathophysiology and genesis of viral and inflammatory diseases[30]. Due to its immune-stimulating and anti-cancer actions, IL-18 has been proposed as a viable adjuvant therapy for cancer[15-17]. However, IL-18 has been linked to the advancement of the disease and in some malignancies, with the likelihood of recurrence and is raised in the blood of the majority of cancer patients[17-19]. It is also addressed how Rhodomyrtone, a bioactive substance found in *Rhodomyrtus tomentosa* leaves, prevents A431 epidermoid carcinoma cells from spreading malignancy[25,26]. In addition, Rhodomyrtone inhibited invasion, migration and metastasis of SW1353 cells, indicating that it has antimetastatic qualities and may one day be employed in antimetastatic therapy[25,26].

CONCLUSION

Giving *Rhodomyrtus tomentosa* at a dose of 400 mg kg^{-1} b.wt., can reduce the expression of PDGF and IL-18 in cervical carcinoma, where the previously uncontrolled carcinoma has now slowed and is no longer evolving into aberrant cells. Through the expression of PDGF-β and IL-18, the molecular mechanism by which Rhodomyrtone produced from *Rhodomyrtus tomentosa* inhibits the spread of cancer has been demonstrated in histological research.

SIGNIFICANCE STATEMENT

This study discovers that *Rhodomyrtus tomentosa* extract can as a herbal for carcinoma cervical problem therapy molecularly. This study will help the researcher to uncover the role of *Rhodomyrtus tomentosa* extract in the molecular signalling of other target proteins for drug development in cancer. Thus, a new theory on the role of *Rhodomyrtus tomentosa* extract in the cervical cancer animal model may be arrived at.

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