ISSN: 0974-3618 (Print)
ISSN: 0974-360X (Online)

Research Journal of Pharmacy and Technology

RJPT

An International Peer-reviewed Journal of Pharmaceutical Sciences

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DOI: *10.52711/0974-360X.2021.00787*

Views: **7** *(pdf),* **3886** *(html)*

Access: *Open Access*

Cite: *A.A. Yaroshenko, V.V. Parchenko, O.A. Bihdan, O.I. Panasenko, Yu V. Karpenko, E.O. Karpun. Method for Trifuzol-Neo assay determination by GC-MS. Research Journal of Pharmacy and Technology. 2021; 14(9):4523-8. doi: 10.52711/0974-360X.2021.00787*

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Cite: *S. Sharmila, S. Preetha, E. Kowsalya, R. Kamalambigeswari, L. Jeyanthi Rebecca. Fermentative extraction of Amylase using waste Biomaterials as Substrate. Research Journal of Pharmacy and Technology. 2021; 14(9):4580-2. doi: 10.52711/0974-360X.2021.00796*

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Access: *Open Access*

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Access: *Open Access*

Cite: *Shaymaa Husham Ahmed, Rand R. Hafidh. The Isolation of specifically lytic phages along with their extracted endolysins as antibacterial agents to MDR Enterococcus faecalis. Research Journal of Pharmacy and Technology. 2021; 14(9):4547-4. doi: 10.52711/0974-360X.2021.00791*

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0974-360X (Online)

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RESEARCH ARTICLE

Role of Claudin-4 and Matrix Metalloproteinase-2 in Tumor Invasion of Colorectal Adenocarcinoma

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ABSTRACT:

Colorectal adenocarcinoma is positioned as the third of most common cancer which the cases rise in Indonesia lately. More than 90% of colorectal carcinoma are adenocarcinoma type. One of prognostic factor of colorectal adenocarcinoma is invasion state of the tumor (T). Uncontrollable proliferation of tumor cell causes transformation of paracellular permeability that increase claudin-4 expression (a protein located on main integral membrane). Claudin-4 activation influence the expression and activity of MMP-2 directly or by altering transduction signal. Expression of claudin-4 and MMP-2 play a role in tumor invasion. Analyzing correlation of claudin-4 and MMP-2 toward invasion state of the tumor (T stadium) on colorectal adenocarcinoma. Analytical observation was conducted on 47 samples of colorectal adenocarcinoma with different invasion state collected by Laboratory of Pathological Anatomy, Dr. Soetomo General Academic Hospital during 2015-2018. Immunohistochemistry was conducted using both claudin-4 and MMP-2 antibodies. Expression of claudin-4 and MMP-2 were semiquantitatively measured then statistically analyzed. Significant result could be obtained in comparison between claudin-4 and tumor invasion state (p=0.773). The significant result could be obtained in comparison between MMP-2 and tumor invasion state (p=0.920). It also could be observed in comparison between claudin-4 and MMP-2 (p=0.638). In summary, claudin-4 and MMP-2 play a role on tumor invasion colorectal adenocarcinoma. It was showed by significant result between claudin-4 and MMP-2 expressions compared to invasion state of colorectal adenocarcinoma.

KEYWORDS: Colorectal adenocarcinoma, claudin-4, MMP-2, invasion state.

INTRODUCTION:

Colorectal cancer is one of malignant cancer in the world which around 1.8 billion new cases are recorded lately[1]. It is positioned as third cancer mostly found, which has high mortality rate (number 4) in the world[2]. Most of colorectal cancer is adenocarcinoma type (98%). According to GLOBOCAN, colorectal cancer is ranked as second deadly cancer for female (614,000 or 9.2% new cases) and third deadly cancer for male (746,000 or 10,0% new cases) around the world.

Mortality rate of colorectal cancer is high in both developed and developing country (10% of mortality compared to other cancer mortality rate)[1]. Case rate of colorectal cancer in Indonesia is high. It leads to mortality around 103,100 (10.2%) of male and 92,200 (8.5%) of female[3]. Data collected by Dr. Soetomo General Academic Hospital, colorectal cancer led to death after lungs cancer in male, and after breast and cervix cancers in female.

Molecular mechanism of colorectal adenocarcinoma has been revealed to understand pathogenicity of its malignancy and one of another way to suggest better prognotion for the patient. Although many researches are conducted to find new prognostic and medication ways, mortality rate of this cancer remains high. One of prognostic factor in collateral adenocarcinoma is state of metastatic according to TNM system[4].

Received on 27.08.2020 Modified on 25.12.2020
Accepted on 12.03.2021
Research J. Pharm. and Tech. 2021; 14(9):4795-4800.
DOI: 10.52711/0974-360X.2021.00834

Severity of colorectal adenocarcinoma could be determined by the range of tumor invasion. According to 8th edition of American Joint Committee on Cancer (AJCC), the prognostic of cancer is getting worse as the tumor cell invades wider area[4]. Tumor invasion is a complicated process which involves many components. These processes are ruled by many biomarker interactions such as claudin-4, a main membrane integral protein located in tight junction (TJ), which is responsible for paracellular permeability and polarity of epithelial cell. Activation of this receptor would activate varies signalling path which involve in tumor invasion[5].

Matrix metalloproteinase (MMP-2) pathway is activated by claudin-4. Matrix Metalloproteinase (MMP-2) belongs to zinc contained enzyme group involved on some extracellular matrix degradation. It plays also role in tumor invasion[6]. Up to now, research focus on correlation between claudin-4 and MMP-2 markers is rarely to be conducted on colorectal adenocarcinoma yet[7,8,9]. This study was conducted to reveal expression of claudin-4 and MMP-2 on colorectal adenocarcinoma to obtain function and relation between both markers in cancer invasion process. This research has been conducted in centre of clinical pathology of Dr. Soetomo General Academic Hospital/Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia.

MATERIAL AND METHODS:

This research used analytical observation method. Samples are consisted of 47 colorectal adenocarcinoma slides which obtained from patients with different grade of tumor invasion, who conducting surgery in Dr. Soetomo General Academic Hospital during 2015-2018. Immunohistochemistry was conducted using claudin-4 and MMP-2 antibodies. The slides were observed used binocular and CX31 Olympus microscopes. Expression of immunohistochemistry was semiqualitative measured and statistically analyzed.

RESULTS AND DISCUSSION:

Basic information such as age, gender, grade and invasion state of the tumor of colorectal adenocarcinoma were collected from 47 patient. According to the age of the patient, colorectal adenocarcinoma commonly suffered by people 60-69 years old (17 cases/36%) compared to people <40 years old and ≥80 years old. According to the gender, male tend to have possibility to suffer colorectal adenocarcinoma (27 cases/57%) than female (20 cases/43%). According to differentiation or grade of colorectal adenocarcinoma, most case was categorized as well differentiated colorectal adenocarcinoma (30 cases/64%). According to the invasion stage, 21 out of cases (45%) categorized as T4.

Table 1: Correlation Between Claudin-4 Expression and Tumor Invasion State.

Statistical/Categorize	Score
Intensity	
Weak	2
Moderate	16
Strong	29
Percentage	
10-50%	3
51-80%	21
>81%	23
IRS score	
Negative	0
Light	2
Moderate	16
Strong	29
Spearman Rho Test	
Correlation Coefficient	0.773**
Sig.(2-tailed)/ρ-value	0.000

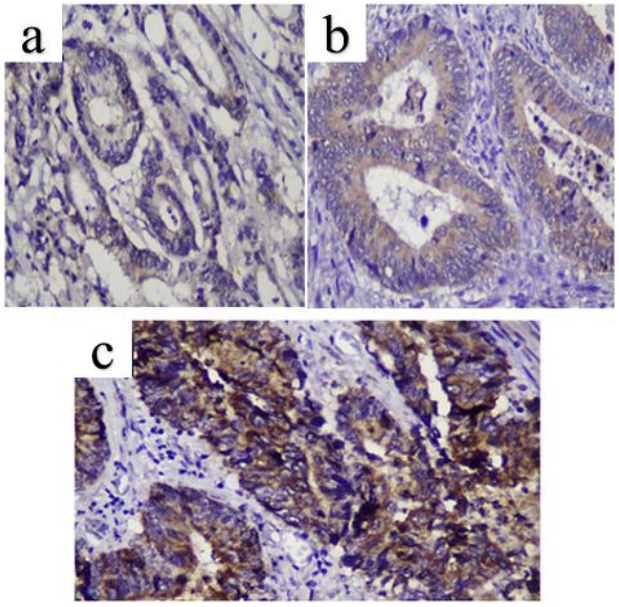

Figure 1: Claudin-4 expression with low intensity (a), moderate intensity (b), and high intensity (c). All figures captured in 400× magnification.

Table 1 showed result 0.773** that means expression of claudin-4 and invasion tumor state has very strong relation. Asterisks (**) means the relation was valued as significant. Coefficient of the correlation had positive value (0.773) means that tumor invasion state rises as the expression of claudin-4 rising. The relation of both variables is irreversible value. Significant value or ρ value is 0.000 and α value is 0.05 (p value <α), thus the hypothesis which said there is significant relation between claudin-4 expression and tumor state invasion on colorectal adenocarcinoma was accepted. The result showed there is strong irreversible significant relation between claudin-4 expression and invasion tumor state of colorectal adenocarcinoma.

Table 2: Relation between MMP-2 expression and tumor invasion state.

Statistics/Categorize	Score
Intensity	
Weak	6
Moderate	18
Strong	23
Percentage	
10-50%	6
51-80%	19
>81%	22
IRS value	
Negative	0
Light	6
Moderate	18
Very strong	23
Spearman Rho Test	
Correlation Coefficient	0.920**
p-value	0.000

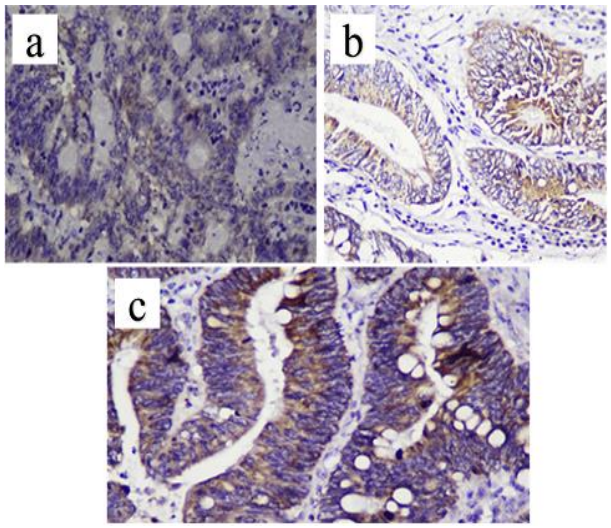

Figure 2: MMP-2 expression with low intensity (a), moderate intensity (b), and high intensity (c). All figures captured in 400× magnification.

Table 2 showed the coefficient correlation was 0.920** that means the correlation between claudin-4 expression and MMP-2 was significantly very strong. The score was positive value which means the correlation between both variables was irreversible. It means the tumor invasion state rises as MMP-2 expression rises. p value is 0.000 and α value is 0.05, (p value <α), thus the hypothesis that said there is significant correlation between MMP-2 and invasion tumor state was accepted. It could be concluded there is very strong irreversible significant relation between MMP-2 and tumor invasion state on colorectal adenocarcinoma.

Table 3: Correlation between claudin-4 expression and MMP-2.

Statistics/Categorize	Score
Spearman Rho Test	
Correlation Coefficient	0.638**
Sig.(2-tailed)/p-value	0.000

Table 3 showed 0.638** of correlation coefficient that means the correlation between claudin-4 expression and MMP-2 was strong. The score of the analysis showed positive value which means the correlation was irreversible thus expression of MMP-2 rises as claudin-4 expression is rising. P-value was 0.000 and α value was 0.05 (ρ value <α), thus hypothesis that said there is significant correlation between claudin-4 expression and MMP-2 on colorectal adenocarcinoma was accepted. According to obtained result there is strong irreversible significant correlation between claudin-4 expression and MMP-2.

The average age of patient who suffered colorectal adenocarcinoma was 59 years old. There were 17 patients (36%) who classified into 60-69 age group. It could be a prove that most colorectal adenocarcinoma attack >50 years old people meanwhile 9% of the case could be found on under 50 years old people[11]. Case rate on younger patient can be related to genetic or chronic intestine inflammation predispositions. New finding from American Cancer Society showed the rising of case rate with 72% suffered by younger people in early 40. The cause of this phenomenon is unclearly yet. Life style, lack of physical exercise, and obesity as the result of unhealthy dietary since childhood and your adult period, were suggested to increase the possibility of younger people suffered colorectal adenocarcinoma. In this research male has tendency to get colorectal adenocarcinoma than female (57%). It proved that prevalence of colorectal adenocarcinoma on male is higher than female[11]. The similar finding was obtained from Dr. Kariadi public hospital Semarang in 2010 which explain that male (58%) tend to suffer colorectal adenocarcinoma than female (42%). It is proved by research conducted by American Cancer Society during 2003-2007 about prevalence and mortality rate of colorectal adenocarcinoma. It is found that male has higher risk (35-40%) to suffer colorectal adenocarcinoma than female[12].

Spearman's Rho test showed the relation of claudin-4 expression and tumor invasion state of colorectal adenocarcinoma. The 0.773 of correlation value means tumor invasion state rising as the claudin-4 expression rises. It is similar to finding that claudin-4 expression could distract tight junction construction thus cancer cell invasion and metastatic rising on colorectal adenocarcinoma case. Claudin-4 is a good biomarker for diagnosing further metastatic risk[13]. Research conducted by Kwon explained that claudin-4 play a role in tumorigenesis. The role of claudin-4 on tumor development relate to the migration, invasion, and metastatic of cancer cell. Recent findings explain that claudin-4 has a role in epithelial to mesenchymal transition (EMT), development of cancer stem cells or

tumor-initiating cells (CSCs/TICs) and chemoresistance. It also suggested that claudin is promised target for tumor medication[14]. Another research conducted by Takehara et al. explained that claudin is not only play a role in distraction of tight junction within cells but also on migration and invasion of cancer cell. Over expression of claudin-4 particularly initiate Caco-2 cell then increasing matrix metalloproteinase-2 (MMP2) activation. Over express claudin-4 in tight junction can be used to evaluate paracellular permeability which set up to measure cell invasion and migration[5]. Dysregulation of claudin-4 expression occurred on transcriptional level and post-transcriptional level. Several proves such as DNA methylation, histone modification or microRNAs (miRNAs) indicate that epigenetic mechanism plays important role in claudin-4 expression regulation. Claudin has role in cancer-promoting or tumor suppressor. Claudin-4 could trigger angiogenesis thus it characterize as pro-angiogenic[14]. Claudin is a main membrane integral protein of tight junction, mainly claudin-4 or so-called claudin permeability. In this research, we investigate the relation of claudin-4 expression and tumor invasion state on colorectal adenocarcinoma. Progression of invasive carcinoma of colon epithelial cells happen for 7-12 years. During this period, many genetic and epigenetic factor activated. In transformation cellular, loss of cell adhesion is important. Tight junction has close functions to cancer cell. It regulates paracellular permeability and loss of cell polarization. Increasing of claudin expression relate to carcinogenesis. Over expression of claudin-4 are detected on many cancers include colorectal adenocarcinoma. 64% of claudin found on colorectal adenocarcinoma relate to deep of tumor invasion which influence the prognostic of the illness. It also proved on research conducted by Suren et al.[15]. Claudin-4 expression relates to further state, poor tumor differentiation, further metastatic state and poor prognostic of colorectal adenocarcinoma. In carcinogenesis, particularly it creates complicated process such as loosen in adhesion, increasing motility and invasion, proteolytic and resistance for apoptotic. Claudin-1, 4 and 7 are important building blocks cell adhesion molecule. Thus, suppressing the expression of cancel cell could effect on cell proliferation, motility, invasion and immune response toward tumor cell[15].

According to the statistical analysis using Spearman's rho test, it is showed there was relation between MMP-2 expression and tumor invasion state of colorectal adenocarcinoma. The coefficient correlation has positive value (0.920). It means the tumor invasion increase as the MMP-2 expression rises. It is noted that over expression of MMP-2 on colorectal adenocarcinoma relate to deep of invasion, nodule metastatic, and relapse[16]. Matrix metalloproteinase (MMP-2) is not expressed on normal colon. It secreted by the tumor cell and stromal cell around the tumor tissue. Particularly, MMP-2 and MMP-9 trigger remodeling module on ECM, regulating proteolytic division, cellular regulation. MMP could be activated by induction of several angiogenic factors such as VEGF, fibroblast growth factor (bFGF), TGF-α and -β and angiogenin. Endothelial cells (EC) could come MMP-2 and MMP-9 vesicles which are stimulated by VEGF and FGF-2 which rule out proteolytic activity that essential for invasion and morphogenic angiogenesis. All MMP will degrade ECM surrounding the tumor tissue, thus invasion and metastatic of tumor cell will be easier. The balance of MMPs/TIMPs are important factor to keep the integrity of ECM and MMP during metastatic state. Tumor metastatic is not depend on concentration of local area MMP but depend on MMPs/TIMPs ratio. If TIMP can not hinder MMP activity, extracellular matrix will be destroyed thus mutation occurred[17]. Several studies showed the essential of MMP serum as the invasion marker on colorectal adenocarcinoma. It is noted that MMP-2 and MMP-9 ratio of colorectal adenocarcinoma patient are higher than normal[16]. Research conducted by Ahmad on 40 sample of colorectal adenocarcinoma tissue revealed the absence of MMP-2 and MMP-9 expression found on normal mucosa (resection margin). It is significantly overexpressed on colorectal adenocarcinoma tissue. It reflects the relation between MMP-2 and MMP-9 expressions and colorectal tumorigenesis. It is noted that MMP expression is controlled by tumor-stromal interaction. This interaction contributes in tumor cell invasion and metastatic. MMP-2 and MMP-9 expressions could be used as target for medication on colorectal adenocarcinoma patient[18]. Matrix metalloproteinase (MMP) is essential on cell proliferation, migration differentiation, angiogenesis, apoptosis, and defense. Matrix metalloproteinase (MMP) increasing processivities and metastatic of invasive cancer by degrading extracellular matrix. Matrix metalloproteinase (MMP-2) and MMP-9 degrade type IV collagen, laminin-5, and help cancer cells metastasize and support tumor development. MMP-9 and other Matrix metalloprotein trigger angiogenesis (essential for tumor) by degrading basement membrane and let VEGF out (angiogenic matter). MMP-9 which located on cell surface is needed for tumor invasion and angiogenesis[19]. The increasing of MMP-2 could degrade extracellular matrix and destroy protein on basalis membrane; thus, tumor cell could enter the stroma and adjacent tissue easier[20]. MT1-MMP (membrane-type MMPs) activate pro-MMP-2 and break type I, II, III collagens, gelatine, fibronectin, laminin-1, vitronectin, cartilage proteoglycans, and fibrillin-1, which expressed by epithelial cell[21]. Both Pro-MMP-2 which is expressed by fibroblast by carcinoma tissue and from serum were caught then activated by carcinoma cell through MT1-

MMP. Over expression of MT1-MMP related to over expression of MMP-2. TIMP-2 is needed to activate pro-MMP-2 by MT1-MMP[22]. TIMP-2 belong to TIMP family which interact to MT1-MMP in MMP inhibition to activate pro-MMP2. TIMP-2 is inhibitor of MMP and is needed for activating pro-MMP2. The balance of MMPs/TIMPs is important factor to keep ECM integrity. Role of MMP on tumor metasthatic is not influenced by absolute concentration of MMP on local area. It is influenced by MMPs/TIMPs ratio. If TIMP could not disturb MMP, the extra cellular matrix will be destroyed, thus invasion occurred. When the MMPs/TIMPs is imbalance, it will lead to ECM degradation. TIMPs may play a role in prognostic and metasthatic factors. The ratio MMP-2/TIMP-2 related to state, infiltration level, and recurrence. MMP-2/TIMP-2 ratio showed invasion and metastatic characteristics more accurate in gall bladder carcinoma than MMP-2 or TIMP-2 expressions respectively[23].

According to Spearman's rho test, it is revealed the relation of claudin-4 and MMP-2 expression in colorectal adenocarcinoma. Coefficient value (0.638) which has positive value showed MMP-2 expression will rises as claudin-2 expression rising. Claudin-4, MMP-2 and MMP-9 expressions which examined from 189 gastric cancer case. Claudin-4 expression has relation to the deep of invasion, lymph glandules metastatic, and lymphatic invasion on gastric cancer. Further analysis showed expression of claudin-4 significantly corelate to MMP-2 and MMP-9 expressions. It is suggested that claudin-4 influence expression and activation of MMP-2 and MMP-9 directly or by modulating transduction signal. Both proteins trigger tumor cell invasion[24]. Over expression of claudin-1 correlate to tumor invasion and metastatic of gastric cancer[25]. Kinugasa et al. showed that the rising of claudin-1 and claudin-2 expressions on colorectal cancer relate to the deep of tumor invasion[26]. Claudin-4 expression has correlation with invasion and metastatic of colorectal adenocarcinoma[13]. It is proved also by Oshima et al. than claudin-7 expression has relation to vena invasion and metastatic on colorectal cancer[27]. According to Usami et al., decreasing of claudin-7 expression in invasive squamous cell esophagus carcinoma could lead to further development and metastatic of tumor[28]. Expression of claudin-4 on ovary epithelial cells might increase invasion and related to increasing od MMP-2 activity[19]. Overexpression of Claudin-4 on colon cancer increase the invasion and activity of MMP-2 and MMP-9[5]. Claudin activity related to MT1-MMP which is needed to activate MMP-2[29]. It marked that claudin is possible increase MMP activity to degrade extracellular matrix and trigger cell motility[30]. Particularly, overexpressed of claudin-4 increase the activity of invasive colorectal cancer. Furthermore, overexpression of claudin-4 could activate matrix metalloproteinase-2 (MMP-2). This finding chowed that invasive activity is stimulated through escalation activity of MMP[5]. Takehara et al. found that Caco-2 cell has overexpression of claudin-4 which proved by escalation of MMP-2 dan MMP-9 activities, compared to faux Caco-2[5].

CONCLUSION:

The research showed irreversible significant relation between claudin-4 and MMP-2 expressions to tumor invasion state of colorectal adenocarcinoma. It is needed to conduct further research to understand more factors which play a role on invasion state of adenocarcinoma. Thus, it could be used for better prognostic and treatment suggestion. It could be used for further research on relation between claudin-4 and MMP-2 expression and another parameter such as KGB regional metastatic

ACKNOWLEDGEMENT:

The author would like to express the gratitude to all lecturers in Department of Anatomical Pathology, Faculty of Medicine, Universitas Airlangga-Dr. Soetomo General Academic Hospital for the guidance, help, and support during the research and manuscript preparation. The Ministry of Health for funding the research through the scholarship grant. We thank Arif Nur Muhammad Ansori for editing the manuscript. We additionally thank Dr. Budi Utomo, dr. M. Kes. for statistical analysis.

CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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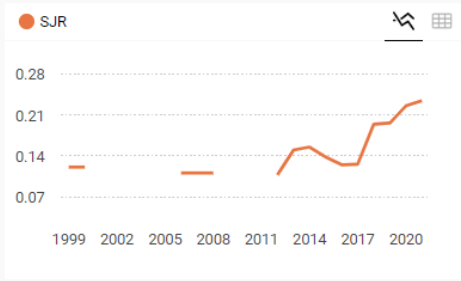

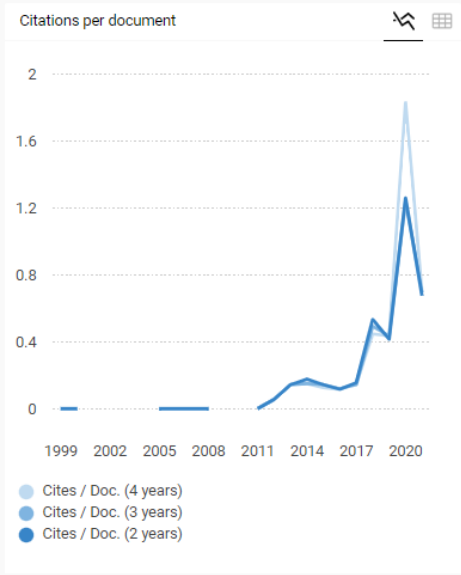

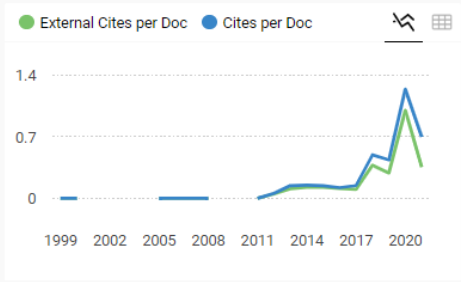

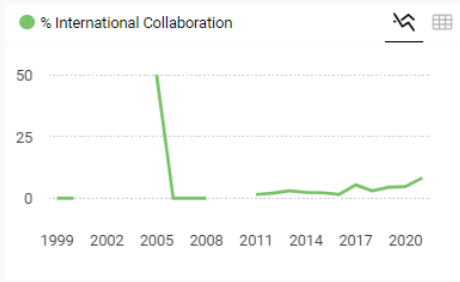

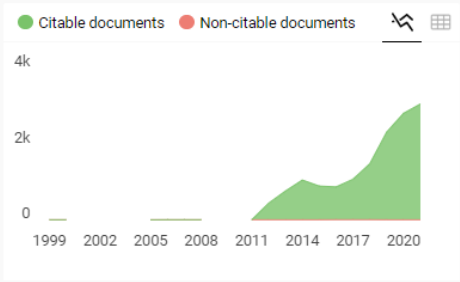

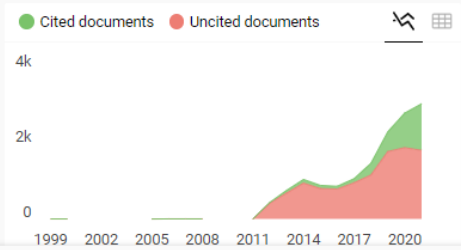

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