Circulatory Cathelicidin Levels' Predictive Value for Pediatric Community-Acquired Pneumonia Without COVID-19

Ahmed Faisal Obed[1], Asmaa Hamza Radeef [2], Hayder Abdul-Amir Makki Al-Hindy[3*], Mazin J. Mousa [4], Omar Taha Hussein[5]

[1]*Ph.D. clinical biochemistry, University of Babylon/ Hammurabi College of Medicine, Babylon, Iraq. ahmed.faisal.obed@gmail.com*

[2]*Ph.D. clinical biochemistry, University of Babylon/ Hammurabi College of Medicine, Babylon, Iraq. asmaa.psb@gmail.com.*

[3]*Medical Physiology, Department of Pharmacology and Toxicology, College of Pharmacy, University of Babylon, Babylon, Iraq. phar.hayder.abdul@uobabylon.edu.iq. Orcid: 0000-0001-6232-8501*

[4]*College of Pharmacy, University of Babylon, Babylon, Iraq. mazin.mousa@gmail.com.*

[5]*Chemistry Dept., College of Science, Al-Nahrain University, Baghdad, Iraq. Omar.Taha@nahrainuniv.edu.iq.*

Abstract: Background: Community-acquired pneumonia (CAP), one of the most common infectious diseases, is the third leading cause of death worldwide. To stop the spread of serious sickness and keep the initial infection under control, the innate immune response is crucial. Cathelicidin, a potent antimicrobial peptide that may kill germs directly and alter the immune system's response to infection, is an essential component of this response. The main goal of the study is to investigate the association between CaLL37 and the severity of CAP in young patients. Methodology: 120 CAP cases and 165 controls made comprised the 285 participants in this case-control study, whose ages varied from 1 to 18 months. Calculated and compared cathelicidin levels for CAP and control participants as well as the pneumonia-causing agent. People who were thought to have COVID-19 CAP were excluded. Results: The participants' mean age was 9.7 (range of 1 to 18) months. In 46.2%, 35%, and 18.8% of cases of CAP; bacterial, viral, and mixed causative agents, respectively, were detected. Among the individuals, only 6.8% received mixed feeding, compared to 42.1% who used artificial feeding and 51.1% who exclusively breastfed. The mean total serum contained 8.6 ±6.7 ng\ml of CaLL37. CaLL37 serum levels were comparable between the two study groups (p>0.05). The levels of CaLL37 were comparable (p>0.05) among patients with CAP when compared according to the causative agents, while plasma CaLL37 levels were higher among babies on artificial feeding (p-0.001). The ROC assays revealed that CaLL37 plasma levels were unable to differentiate between bacterial and viral pneumonia or between persons who had pneumonia and healthy subjects. However, the CaLL37 can discriminate between infants who are breastfed and those who are fed by a bottle considerably (p-0.001, AUC=0.748, sensitivity=0.673, specificity=0.637, and 95%CI of o.675 - 0.820). Conclusion: According to the study, CaLL37 is capable of determining the difference between infants who are breastfed and those who are fed artificially. However, it is difficult for cathelicidin to distinguish between various CAP causes as well as between CAP patients and healthy controls.

Keywords: Pediatric Pneumonia, Cathelicidin, LL37, Community-Acquired.

1. INTRODUCTION

In December 2019, Wuhan, China, reported an outbreak of atypical pneumonia that could be fatal. This outbreak was labeled "coronavirus disease 2019 (COVID-19)" (1-3).

Community-acquired pneumonia (CAP), one of the most common infectious diseases, is the third leading cause of death worldwide. Its epidemic characteristics vary according to the immune system and distribution of the host, and related pathogen spectrums shift throughout time and space. In the meantime, the COVID-19 pandemic has led to an increase in the usage of several innovative therapeutic strategies (4).

The response of the innate immune is essential for containing the initial infection and inhibiting the development of serious illness. A crucial element of this response is cathelicidin, which functions as a powerful antimicrobial peptide that can both directly kill microorganisms and modify the immune response to infection (5).

Although there are several beta-defensin genes in the human genome, only one gene for cathelicidin (CAMP) has been identified in humans (6). LL-37 is produced by proteolytic cleavage of the specific human cathelicidin (hCAP18), which has a molecular weight of 18 kDa and only cleaves into the cathelin domain and "cathelicidin-derived AMP"(7).

Only LL-37(8), an AMP created from human cathelicidin, is secreted by the mammary glands and found in human milk.

According to studies that have shown reduced cathelicidin levels in people with CAP, low levels of cathelicidin LL37 have been connected to unfavorable outcomes in patients with pneumonia. Additionally, pneumonia patients with low cathelicidin levels are more likely to require hospitalization, have more severe forms of the illness, and have a higher risk of dying from the condition (9, 10).

There is evidence to suggest that the cathelicidin pathway could be a focus of future CAP treatments. For instance, studies have demonstrated that administering artificial cathelicidin analogs to animals with pneumonia can enhance the results. The use of cathelicidin in the treatment of CAP has drawn more attention in recent years. Additionally, it has been demonstrated that the use of cathelicidin-stimulating substances, such as probiotics, might raise cathelicidin levels and enhance outcomes in CAP patients (5,12).

More research is required to comprehend the role of cathelicidin in the pathophysiology of CAP and to develop effective therapeutics based on this pathway. To determine the optimum therapy dosage and duration as well as the safety and effectiveness of these interventions in larger patient populations, more study is needed.

The main aim of the study was to examine the correlation between CaLL37 and the severity of CAP in children, as well as its prediction.

2. MATERIALS AND METHODS

120 pneumonia patients and 165 healthy controls made comprised the 285 participants in this multicenter, case-control experiment, whose ages varied from 1 to 18 months. Children's hospitals in Babylon, Iraq, received the kids between September 2020 and February 2021. To diagnose and treat children with CAP, pediatricians performed a history review, clinical examination, blood tests, and chest X-rays. Each pneumonia patient had data on their age, sex, feeding method, and length of illness collected as well. Complete blood was collected from each subject, the CaLL37 and WBC levels were computed, and the pneumonia-causing agent was identified using simple test tubes.

The American programme SPSS-23 was used to do the descriptive statistics. Based on feeding type characteristics, the descriptive data (means and standard deviation) for cathelicidin, WBCs, causative agents, and infant count were computed. The "Shapiro-Wilk test" was used to determine whether the distribution was normal. The Mann-Whitney test, Students' T-test, and ANOVA were used, respectively, to determine the relationships between the blood levels of cathelicidin, ages, and WBCs. Spearman's correlation was used to show the relationships between the research groups' serum CaLL37 concentrations. Statistics were considered significant at p-0.05. The ability of ROC analysis to forecast CAP in healthy participants was examined.

The American programme SPSS-23 was used to do the descriptive statistics. Based on feeding type characteristics, the descriptive data (means and standard deviation) for cathelicidin, WBCs, causative agents, and infant count were computed. The "Shapiro-Wilk test" was used to determine whether the distribution was normal. The Mann-Whitney test, Students' T-test, and ANOVA were used, respectively, to determine the relationships between the blood levels of cathelicidin, ages, and WBCs. Spearman's correlation was used to show the relationships between the research groups' serum CaLL37 concentrations. Statistics were considered significant at p-0.05. The ability of ROC analysis to forecast CAP in healthy participants was examined.

3. RESULTS

The key characteristics of the study participants are outlined in Table (1). The participants' ages ranged from 1 to 18 months, with an average age of 9.7 months. In this investigation, there was no indication of a sex bias. The mean total WBC counts were within the usual range of 6.8 3.5 x 103. In 46.2%, 35%, and 18.8% of cases of pneumonia, bacterial, viral, and mixed causative agents, respectively, were detected. Only 6.8% of the participants got mixed

feeding, whereas 51.1% exclusively breastfed and 42.1% used artificial feeding. The mean total serum contained 8.6 6.7 ng/ml of CaLL37.

Table 1: The main characteristic features of the total studied participants

Variables	Descriptives		Min – Max
Ages (Mean ±SD)	Months	9.7 ± 6	1 – 18
Gender N (%)	Males	138 (48.4)	
	Females	147 (51.6)	
WBCs (Mean ±SD)	$1x10^3$	6.8 ± 3.5	6.08 – 17.3
Causative agents N (%)	Bacterial	55 (46.2)	
	Viral	42 (35.0)	
	Mixed	23 (18.8)	
Types of feeding N (%)	Breast	120 (42.1)	
	Artificial	146 (51.1)	
	Mixed	19 (6.8)	
Cathelicidin (Mean ±SD)	ng/ml	8.6 ± 6.7	0.6 – 37.1

While age and CaLL37 serum levels were comparable between the two groups (p>0.05), the total WBC numbers in the pneumonia group were substantially higher.

Table 2: Variations in the plasma Cathelicidin levels, age, and WBCs, between the two study groups

Variables	Pneumonia (N-120)	Healthy (N-165)	Significance
Ages (Months)	10.4 ± 12.8	9.2 ± 7.7	> 0.05
WBCs	8.6 ± 3.5	6.3 ± 1.5	0.001
Cathelicidin (ng/ml)	9.4 ± 6.9	8.1 ± 6.6	> 0.05

Ages, WBCs, and CaLL37 circulating levels all showed non-significant gender differences (Table 3).

Table 3: Variations in the plasma Cathelicidin levels, age, and WBCs, according to gender

Variables	Males (N-110)	Females (N-80)	Significance
Ages (Months)	8.8 ± 9.8	10.6 ± 10.4	> 0.05
WBCs	7.2 ± 2.6	7.4 ± 2.9	> 0.05
Cathelicidin (ng/ml)	8.3 ± 6.5	8.9 ± 6.9	> 0.05

According to the causative agents, individuals with CAP's mean circulatory CaLL37 levels were comparable (p>0.05) (Table 4).

Table 4: Serum cathelicidin levels among patients with community-acquired pneumonia change based on the etiology of pneumonia

Descriptives	Mean	Std. Deviation	Significance
Bacteria	9.37	6.9	> 0.05
Virus	8.8	4.9	
Mixed	10.75	9.4	

The neonates' WBC in the two study groups did not alter as a result of breast or artificial feeding, but plasma CaLL37 levels were greater in infants receiving artificial feeding (p-0.001), as shown in Table 5.

Table 5: The variations in the WBCs, and plasma Cathelicidin levels according to types of feeding

Variables	Breast	Artificial	P-value
WBCs	6.8 ± 2.4	7.4 ± 2.4	> 0.05
Cathelicidin (ng/ml)	5.8 ± 6.2	10.6 ± 6.6	0.001

The CaLL37 plasma levels could not differentiate between bacterial and viral pneumonia, or between patients with pneumonia and healthy participants, according to the ROC assays [AUC=0.579, sensitivity =0.402, specificity =0.575, and P>0.05]. However, the CaLL37 can tell a lot of difference between babies who are breastfed and those who are fed by the bottle (p-0.001, AUC=0.748, sensitivity=0.673, specificity=0.637, and 95%CI of o.675 - 0.820); Table 6.

Table 6: The area under the curve (AUC) for serum Cathelicidin (ng/ml) levels to predict pneumonia from healthy controls, bacterial from viral community-acquired pneumonia, and those on a bottle from breastfeeding

Ability to predict	AUC	Sensitivity	Specificity	Sig.	95% CI
Pneumonia from healthy controls	0.579	0.515	0.575	0.064	0.497 – 0.660
Bacterial from viral pneumonia	0.509	0.402	0.512	0.906	0.364 – 0.654
Bottle from breastfeeding	0.748	0.673	0.639	0.001	0.675 – 0.820

4. DISCUSSION

Data on cathelicidin LL-37 expression during CAP in pediatric age groups are few. This investigation attempted to calculate the connection between blood CaLL37 levels and non-COVID CAP in a case-control study. The main conclusion of the current study was that cathelicidin had a strong ability to discriminate between breast-fed and artificially fed newborns, despite having a weak ability to distinguish between patients with pneumonia and healthy individuals. Between the two study groups, there were no detectable differences in the serum CaLL37 concentrations that were related to CAP etiology.

A growing body of research has shown results that are comparable to the ones of the current study. Recent studies have shown that the fermented artificial formula stimulates intestine production of innate immunopeptides, including human cathelicidin LL-37, which protect against infectious illnesses.

Similar to the earlier discovery, fermented formula can boost antimicrobial activity, which may explain why toddlers who consumed such formula had higher fecal antimicrobial immunopeptide levels (13).

Another explanation for the higher levels of CaLL37 in artificially fed newborns compared to breastfed infants could be vitamin D contributing functions. CaLL37 and vitamin D (15) show a link between pathogenic inflammation and protective immunity after infection. Vitamin D is necessary for the metabolism of calcium and phosphorus, according to a growing body of studies (16–18).

In recent years, it has been demonstrated that many supplements, including vitamin D3, significantly increase host defense expression. Since human milk contains less vitamin D than infant formula, pediatricians are aware that infants who are exclusively breastfed need to take vitamin D supplements(19).

Contrary to the results of this study, mounting evidence indicates that newborn infants with pulmonary infections and inborn pneumonia had significantly higher serum levels of LL-37 (20) and elevated LL-37 measures in tracheal aspirates (20, 21) compared to healthy controls. Infants with post-infection bronchiolitis obliterans were reported to have higher amounts of circulating LL-37 than controls (22). Adult patients with pulmonary tuberculosis also reported greater levels of circulating LL-37 compared to healthy individuals (23).

"hCAP18/LL-37 mRNA expression" in human mammary cells was confirmed and grew between 30 and 60 days after birth. Furthermore, western blot research showed that mothers of both full-term and preterm infants had maternal milk that contained CaLL37, which was secreted and abundant in the matured peptide form in breast milk (24).

The signaling lipid "sphingosine-1-phosphate (S1P)" upregulates the "NF-B-C/EBP-dependent transcriptional machinery" for CAMP in epithelial cells (25, 26). Importantly, under these conditions, vitamin D receptor transactivity is inhibited (25), whereas this pathway only activates following cellular exposure to exogenous variation. Endoplasmic reticulum stress results from this fluctuation, demonstrating that these binary mechanisms control CAMP levels in epithelial cells under circumstances that predominate under stressful situations as opposed to basal conditions. Additionally, recent studies have demonstrated that dietary "stilbenoid resveratrol" boosts CAMP production via the S1P-mediated channel (27).

Numerous functions of epithelial LL-37 include selectively increasing and attenuating particular features of the inflammatory response (28). When neutrophils, dendritic cells, T cells, macrophages, and monocytes are stimulated by infections, it acts as a chemokine to help them (29). Interleukins (ILs) are essential pro-inflammatory cytokines that are important in pulmonary systemic and local inflammation (30, 31). LL-37 and IL-1 work together to boost the local production of inflammatory cytokines. Other pleiotropic cytokines with multicellular activity include "Transforming growth factor-beta (TGFB)" (32, 33). Age-related reductions in cathelicidin production in response to infection were brought about by a drop in the number of antimicrobial peptides after birth.

TGF- was discovered to be a significant upstream regulator of this process since it interfered with uncommitted adult and embryonic agents' capacity to function as antimicrobials. Furthermore, inhibiting the TGFB receptor increased the resistance of adult mice to S. aureus infection and recovered the antibacterial function (34).

Nevertheless, the impact of human cathelicidin on innate immunity is not well understood by experts. Additional well-crafted randomized clinical trials are strongly required to completely understand the unique effects of human cathelicidin LL37 on the etiology of pneumonia in pediatric and adult ages.

CONCLUSION

The ability of Cathelicidin to distinguish between various CAP causes as well as between CAP patients and healthy controls is marginal. CaLL37 can identify between infants who are breastfed and those who are fed artificially.

Declaration of Interests

Grants from two companies: Nutridar® and Evolac-Iraq® were given to Hayder. The disclosed financial interests, according to Hayder, have no influence on the work that has been submitted. There are no other competing interests to declare for the author. In addition, the funders played no part in the design of the study, collecting and analyzing of the data, or the choice to submit the work for publication.

REFERENCES

1. Amal Talib Al Sa'ady ZAA, Ali Fadhil Obaid, Amir S. Al-Mumin Prevalence of adverse effects from COVID-19 vaccine among Iraqi adults: A retrospective cross-sectional study. Journal of Emergency Medicine, Trauma Acute Care. 2022;3(6):1-9.
2. Hayder AA, Mazin JM, HO Hashim. BCG Vaccine in preventing COVID-19 epidemic had to be reviewed: correlation does not imply causation. Australian Journal of Basic and Applied Sciences. 2021;14(11):58-63.
3. Hajir Karim Abdul-Husseein KAA-A, Mustafa Karim Abdul-Husseein. The Liver Function Abnormalities in COVID-19 Patients and Their Association with Age and Sex: A Cross-Sectional Study. Archives of Razi Institute. 2022;77(5).
4. Jiang N, Long, Q. Y., Zheng, Y. L., Gao, Z. C. Advances in epidemiology, etiology, and treatment of community-acquired pneumonia. Chinese Journal of Preventive Medicine. 2023;57(1):91-9.
5. Scheenstra MR, van den Belt M, Tjeerdsma-van Bokhoven JLM, Schneider VAF, Ordonez SR, van Dijk A, et al. Cathelicidins PMAP-36, LL-37, and CATH-2 are similar peptides with different modes of action. Scientific Reports. 2019;9(1):4780.
6. Kościuczuk EM, Lisowski P, Jarczak J, Strzałkowska N, Jóźwik A, Horbańczuk J, et al. Cathelicidins: a family of antimicrobial peptides. A review. Molecular biology reports. 2012;39(12):10957-70.
7. Dürr UH, Sudheendra US, Ramamoorthy A. LL-37, the only human member of the cathelicidin family of antimicrobial peptides. Biochimica et Biophysica Acta. 2006;1758(9):1408-25.

8. Murakami M, Tonouchi H, Takahashi R, Kitazawa H, Kawai Y, Negishi H, et al. Structural analysis of a new anti-hypertensive peptide (beta-lactosin B) isolated from a commercial whey product. Journal of dairy science. 2004;87(7):1967-74.
9. Rima M, Rima M, Fajloun Z, Sabatier J-M, Bechinger B, Naas T. Antimicrobial Peptides: A Potent Alternative to Antibiotics. 2021;10(9):1095.
10. Burkes RM, Ceppe AS, Couper DJ, Comellas AP, Wells JM, Peters SP, et al. Plasma Cathelicidin is Independently Associated with Reduced Lung Function in COPD: Analysis of the Subpopulations and Intermediate Outcome Measures in COPD Study Cohort. Chronic obstructive pulmonary diseases (Miami, Fla). 2020;7(4):370-81.
11. Lee JH, Kim, Y. M., Kim, E. J., Kim, H. J., Lee, J. H., Song, J. H., et al. Low expression of cathelicidin in patients with community-acquired pneumonia is associated with increased severity and poor outcome. Tuberculosis and respiratory diseases. 2012;72(1):66-72.
12. Cebrián R, Xu C, Xia Y, Wu W, Kuipers OP. The cathelicidin-derived close-to-nature peptide D-11 sensitizes Klebsiella pneumoniae to a range of antibiotics in vitro and in vivo. International Journal of Antimicrobial Agents. 2021;58(5):106434.
13. Nocerino R, Paparo L, Terrin G, Pezzella V, Amoroso A, Cosenza L, et al. Cow's milk and rice fermented with Lactobacillus paracasei CBA L74 prevent infectious diseases in children: A randomized controlled trial. Clinical nutrition (Edinburgh, Scotland). 2017;36(1):118-25.
14. Corsello G, Carta M, Marinello R, Picca M, De Marco G, Micillo M, et al. Preventive Effect of Cow's Milk Fermented with Lactobacillus paracasei CBA L74 on Common Infectious Diseases in Children: A Multicenter Randomized Controlled Trial. Nutrients. 2017;9(7).
15. Chung C, Silwal P, Kim I, Modlin RL, Jo EK. Vitamin D-Cathelicidin Axis: at the Crossroads between Protective Immunity and Pathological Inflammation during Infection. Immune network. 2020;20(2):e12.
16. AL-Shimmery AHS, Mahdi, Zena Abdul-Ameer, Al-Mammori, Raheem Tuama Obayes, Mokif, Thanaa Abdulmahdi, Al-Dahmoshi, Hussein O M, Al-Khafaji, Noor S K Immunological Study of IFN-γ, ICAM-4, and Vitamin D3 Markers among Gastrointestinal Tumor Patients in Babylon Province, Iraq. The Asian Pacific Journal of Cancer Prevention. 2023;24(1):253-7.
17. Masser JA-H, Mousa MJ, Makki HA-A, Al-Khafaji NSK, Al-Dahmoshi HOM, Mahdi ZA-A, et al. Calcium and Phosphate Homeostasis in Patients with Recurrent Nephrolithiasis. Journal of Contemporary Medical Sciences. 2021;7(6).
18. Ghazi Mohamad Ramadan SRO, Hussein Ali Abdulabbas. Assessment of Serum Vitamin D in Transfusion-Dependent B-Thalassemia Patients: Single-Center Observational Study. History of medicine. 2023;9(1).
19. Kim YJ. Comparison of the serum vitamin D level between breastfed and formula-fed infants: several factors that can affect serum vitamin D concentration. Korean Journal of Pediatrics. 2013;56(5):202-4.
20. Gad GI, Abushady NM, Fathi MS, Elsaadany W. Diagnostic value of anti-microbial peptide, cathelicidin in congenital pneumonia. The Journal of maternal-fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2015;28(18):2197-200.
21. Schaller-Bals S, Schulze A, Bals R. Increased levels of antimicrobial peptides in tracheal aspirates of newborn infants during infection. American Journal of Respiratory and Critical Care Medicine. 2002;165(7):992-5.
22. Yu J. Postinfectious bronchiolitis obliterans in children: lessons from bronchiolitis obliterans after lung transplantation and hematopoietic stem cell transplantation. Korean Journal of Pediatrics. 2015;58(12):459-65.
23. Zhan Y, Jiang L. Status of vitamin D, antimicrobial peptide cathelicidin and T helper-associated cytokines in patients with diabetes mellitus and pulmonary tuberculosis. Experimental and therapeutic medicine. 2015;9(1):11-6.
24. Murakami M, Dorschner RA, Stern LJ, Lin KH, Gallo RL. Expression and secretion of cathelicidin antimicrobial peptides in murine mammary glands and human milk. Pediatric research. 2005;57(1):10-5.
25. Park K, Elias PM, Oda Y, Mackenzie D, Mauro T, Holleran WM, et al. Regulation of cathelicidin antimicrobial peptide expression by endoplasmic reticulum (ER) stress signaling, vitamin D receptor-independent pathway. The Journal of Biological Chemistry. 2011;286(39):34121-30.
26. Park K, Elias PM, Shin KO, Lee YM, Hupe M, Borkowski AW, et al. A novel role of a lipid species, sphingosine-1-phosphate, in epithelial innate immunity. Molecular and cellular biology. 2013;33(4):752-62.
27. Park K, Kim YI, Shin KO, Seo HS, Kim JY, Mann T, et al. The dietary ingredient, genistein, stimulates cathelicidin antimicrobial peptide expression through a novel S1P-dependent mechanism. The Journal of Nutritional Biochemistry. 2014;25(7):734-40.
28. Lecaille F, Lalmanach G, Andrault PM. Antimicrobial proteins and peptides in human lung diseases: A friend and foe partnership with host proteases. Biochimie. 2016;122:151-68.
29. Leiva-Juárez MM, Kolls JK, Evans SE. Lung epithelial cells: therapeutically inducible effectors of antimicrobial defense. Mucosal Immunology. 2018;11(1):21-34.
30. Amjed H. Abbas, Mazin J. Mousa, Hadeel Abd Ameir Al-Shalah. The Role of Serum IL-1β in Combination with Fractional Exhaled Nitric Oxide in the Diagnosis of Adult Bronchial Asthma. NeuroQuantology. 2021;19(8):13-9.
31. Hayder Makki, Ali JH, Mazin J. Mousa, Safa Jihad Hameed, Suhad Hafidh Obeed. The Utility of Serum IL-1β and CRP Together with Fractional Exhaled Nitric Oxide in the Diagnosis of Asthma in Adults. NeuroQuantology. 2021;19(8):119-24.
32. Ghazi Mohamad Ramadan, Mazin Jaafar Mousa, Hafidh I. Al-Sadi Evaluation of Transforming Growth Factor-Beta 1 (TGFβ1) Levels in Cases with Multiple Myeloma: Case-Control Study among Iraqis. Journal for ReAttach Therapy Developmental Diversities. 2022;5(2s):516-23.

33. Mazin J. Mousa HSAS, Hayder Abdul-Amir Maki Al-Hindy. Low-Level Laser (Biophotomodulation) Therapy for the Treatment of Diabetic Foot Ulcers with 532 nm KTP Laser Induces Wound Healing, Fibroblast Proliferation, and Over-expression of TGF. Systematic Review In Pharmacy. 2020;11(5):396-403.

34. Zhang L-j, Chen SX, Guerrero-Juarez CF, Li F, Tong Y, Liang Y, et al. Age-Related Loss of Innate Immune Antimicrobial Function of Dermal Fat Is Mediated by Transforming Growth Factor Beta. Immunity. 2019;50(1):121-36.e5.

DOI: https://doi.org/10.15379/ijmst.v10i4.2803