Anticancer potential from *Rhizophora mucronata* plant leaf associated *Streptomyces* species against the breast cancer cell line

ABSTRACT

INTRODUCTION: *Rhizophora mucronata* is a small to medium sized evergreen tree growing to a height of about 20 to 25 meters (approximately 66 to 82 feet), on the banks of river. These mangroves have anticancer, antioxidant, antifungal, and viral activities which enhances its existence. *Streptomyces* species are the largest genus of Actinobacteria. They are gram positive and are found in soil, decaying vegetation and mangrove leafs. The breast cancer cell lines are used to test the anticancer potential.

AIM: Aim of the study was to assess the antibacterial activity from Rhizophora mucronata, against breast cancer cell line.

MATERIALS AND METHODS: Collection of *Rhizophora mucronata* (a mangrove species) followed by *Streptomyces* from mangrove leaf, preparation of extract with characterisation features positive for *Streptomyces* and MTT assay to check the anticancer potential.

RESULTS AND DISCUSSION: The *Rhizophora mucronata* was identified by colour of aerial mycelium, soluble pigments, Spore chain morphology. Further, the Arabinose enzyme production was done and estimated also completed. The potential antimicrobial activity from the *Streptomyces* metabolites was done. Zone of inhibition and MIC were calculated.

CONCLUSION: *Rhizophora mucronata* mangrove plant leaf associated Maine *Streptomyces* shows good anti cancer activity. Further detailed calculations and future study is possible using the species.

Keywords- *Rhizophora mucronata, Streptomyces* species, Anticancer potential, Novel drug

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INTRODUCTION

Mangroves are defined as woody trees and shrubs that grow in marshy areas(1). These plants have adapted themselves morphologically and physiologically to the habitat which has salinity, high tidal inundation as well as high wind velocity complex. Plants belonging to this genus are very effective in producing phytochemicals and metabolites, thus have high medicinal potential. Mangroves are tremendously used in the arena of traditional medicine. The leaves, roots, and bark of these mangroves are used for the treatment of hemorrhages, angina as well as hematuria(2).

Rhizophora mucronata has various benefits as antiviral and antibacterial, cytotoxic, analgesic and diuretic activities(3). Mangrove plants are halophyte plants seen in tropical and subtropical areas in some parts of the world. Different chemical compounds and metabolites associated with the plants are extracted for various properties(4).

Streptomyces is the largest genus of actinobacteria, belonging to the type of the genus of the family Streptomycetaceae(5). These are gram-positive bacteria, belonging predominantly to the soil and decaying vegetation. Streptomycetes are characterized by various complex secondary metabolism. They produce over two-thirds of the clinically useful antibiotics from their natural origin. In recent years, the service by the biotechnology researchers have begun using Streptomyces species for heterologous expression of proteins(6).

Cancer is the deadly disease that affects different organs, and is identified by the unchecked proliferation of abnormal cells that invade other healthy tissue, associated with various regulation of cell cycles and apoptosis processes(7). The treatment is primarily confined to the chemotherapy process. Besides being an expensive process, chemotherapy is known for various severe side effects to the patient's body, making treatment problematic eventually. For medicinal chemists, the primary goal still remains hidden with the discovery and identification of various chemotherapeutic agents derived from natural products(8). Despite numerous researches from past decades and effective treatment for deadly disease cancer is still lacking, therefore there is a great need for newer compounds having anticancer potential including the cell selective activities with reduced adverse effects. Secondary metabolites derived from various flora like that of

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Rhizophora mucronata have opened new avenues for the development of novel therapeutic agents., Plant derived compound is now considered as the most effective and crucial method. Research scientists have identified many other crucial anticancer molecules from fungal endophytes of mangrove plants(9). Many researchers were attracted to marine mangrove fungi because of their diversity, which may lead to the discovery of several novel natural products to society. With the remarkable advancements that occurred in the spectroscopic techniques, along with the separation methods and microplate-based sensitive in vitro assays, the natural product exploration of mangrove fungi has attracted special attention regarding novel and unexplored chemical substances associated with it.

Breast cancer cell lines have been widely used for the process of breast cancer modelling which encompassess a panel of diseases using distinctive phenotypic associations. Hence, the main aim of the study is to evaluate the anticancer potential from Rhizophora mucronata plant leaf associated Streptomyces species, against the breast cancer cell line(10). Further, our team has extensive knowledge and research experience that has translated into high quality publications(11–15),(16),(17),(18),(19),(20),(21),((13,22,23),(24–28),(29),(30). Aim of the study was to assess the antibacterial activity from *Rhizophora mucronata*, against breast cancer cell line.

MATERIALS AND METHODS

The sediment sample was collected from the Pitchavaram coast of Tamil Nadu. The collected sample was sun dried for 48 hours and turned into fine powder by mortar and pestle. Isolation of Streptomyces from mangrove leaves. preparation of extract was done and characterization of features positive for *Streptomyces*. MTT assay to check the anticancer potential. The study was done in the Blue Lab, Saveetha Dental College and Hospital.

RESULTS

The results obtained confirmed that *Rhizophora mucronata* associated *Streptomyces* were isolated from the sediment samples. They were confirmed by the features as colour of the aerial mycelium as white, soluble pigment present and spiral spore chains. In case of assimilation of carbon source- inositol, mannitol, arabinose, rhamnose, sucrose and raffinose were positive. This is illustrated in Table 1. Various cell wall amino acids were present including LL-DAP and glycine as well as cell wall type as 1. Table 2 illustrates the same features of the cell wall. Colour

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of aerial mycelium is considered to be white (figure 1) and spore chain as spiral (figure2) are certain positive features.

MTT assay was done for various drug concentrations. In the control for 24hours the cell viability was maximum. When the drug concentration increases the cell viability decreases as the breast cancer cell line dies eventually. The results was illustrated in Figure 3 & 4 depicts the cell viability before and after the addition of secondary metabolites.

Figure 1: White colour of aerial mycelium of *Streptomyces*

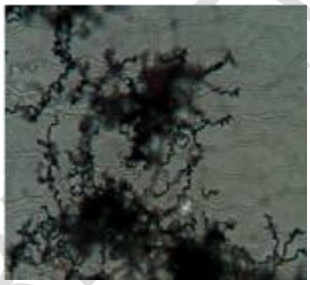

Figure 2: Spiral spore chain

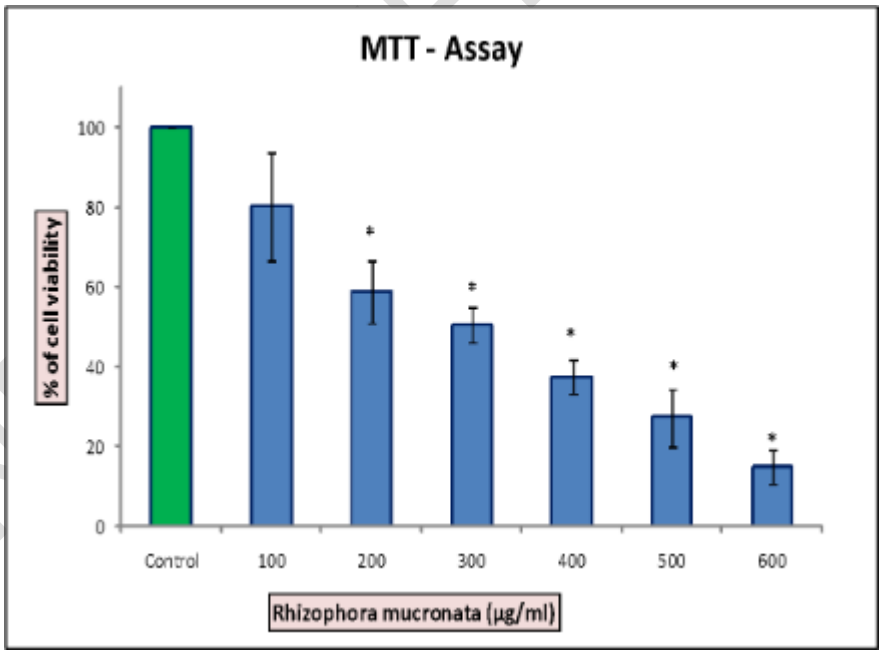

Figure 3: Demonstration of Drug concentration in MTT assay

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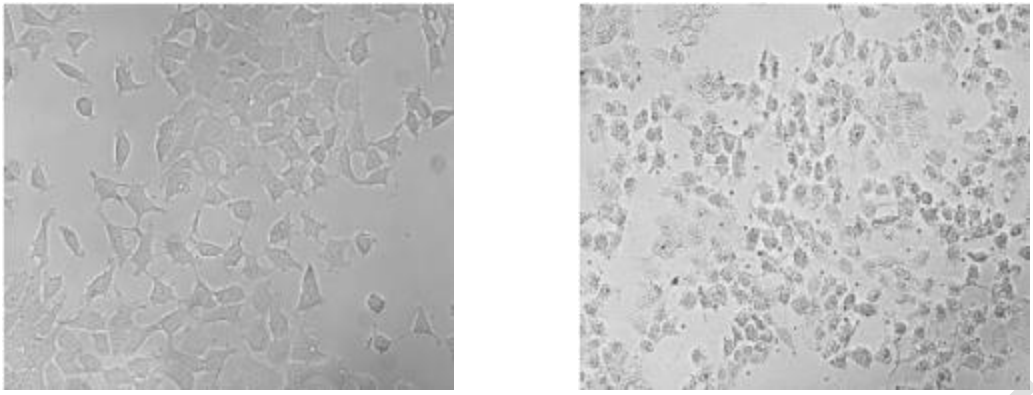

Control Treated

Figure 4: Figure depicting the cell viability before and after the addition of secondary metabolites

Table 1: Conventional Identification of Mangrove associated *Streptomyces* species

FEATURES	PRESENCE/ ABSENCE
Colour of aerial mycelium	White
Melanoid pigment	-
Soluble pigment	+
Reverse side pigment	-
Spore chain	Spiral
ASSIMILATION OF CARBON SOURCE	
Arabinose	+
Xylose	-
Inositol	+
Mannitol	+
Fructose	-
Rhamnose	+
Sucrose	+
Raffinose	+

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Table 2: Cell wall and sugar pattern analysis of *Streptomyces* sp

INDEX	STREPTOMYCES	
Cell wall type	1	
Cell wall amino acids	LL-DAP MesoDAP Glycine	+ - +
Cell wall sugar	Arabinose Galactose	- -

DISCUSSION

Marine actinobacterial *Rhizophora mucronata* showed potential anticancer activity against all other anticancer studies when compared to other studied organisms. It can be comprehended from various studies that there is still a very little understanding of diversity in this genus. The results confirmed that *Rhizophora* sp associated marine *Streptomyces* (Table 1) metabolites have good anti cancer potential. The *Streptomyces* species were verified by the white color of the aerial mycelium. In addition to that, there were positive readings for soluble pigments, arabinose, inositol, mannitol, rhamnose and there were negative readings for melanoid pigment, reverse side pigment, xylose and fructose. Marine populations represent reservoirs of novel bioactive metabolites with diverse groups of chemical structures. Therapeutic strategies and the present use of marine natural products components, its future direction and limitations are discussed by Khalifa et al., (31). Actinobacteria still a source of novel antibiotics (32). There are more than 22,000 known microbial secondary metabolites, 70% of which are produced by actinomycetes, 20% by fungi, 7% by *Bacillus* spp. and 1–2% by other bacteria (33). Some of these bioactive compounds are antimicrobial agents, whereas dibutyl phthalate and di-(2-ethylhexyl) phthalate have been reported to be cathepsin B inhibitors (34). Discodermolide, bryostatins, sarcodictyin, and eleutherobin are among the most effective anticancer drugs produced mainly by marine bacteria (35,36). In the exploration of marine-derived actinomycetes as sources of antitumor compounds, lucentamycins A-D, which are 3-methyl-4-ethylideneproline-containing peptides were isolated from *Nocardiopsis lucentensis* (strain CNR-712). Lucentamycins A and B exhibited significant in vitro cytotoxicity against HCT-116 human colon carcinoma using MTS assay with IC_{50} = 0.20 and 11 µM, respectively (37).

CONCLUSION

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Mangrove fungi are considered to be a ubiquitous source of novel bioactive metabolites with the potential to display anticancer properties as a major property. The phenomenon is greatly observed in mangrove fungal metabolites, as they show potent anticancer activity via different mechanisms of action such as apoptotic cell death, the inhibition of kinase proteins involved in signal transduction pathways and the destruction of cell wall protein. Although many metabolites demonstrated moderate cytotoxic activities against cancer cell lines, only a few displayed superior activity than the standard anticancer drugs. It can be suggested that the rational derivatization of secondary metabolites may provide molecules with better activity against a wide range of breast cancer cell lines. In addition, the identified secondary metabolites with broad-spectrum anticancer activity need to be investigated to establish their mechanisms of action and to develop as novel anticancer therapeutic agents in future(27) (31) (32) (33) (34) (35) (36) (37) (38) (39) (40) (41) (42) (43) (44). Rhizophora mucronata mangrove plant leaf associated Streptomyces shows good anti cancer activity. Further detailed calculations and future study is possible using the species.

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COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

REFERENCES

1. Deshmukh SK, Gupta MK, Prakash V, Reddy MS. Mangrove-Associated Fungi: A Novel Source of Potential Anticancer Compounds. J Fungi (Basel) [Internet]. 2018 Aug 24;4(3). Available from: http://dx.doi.org/10.3390/jof4030101

2. Khajure PV, Rathod JL. Potential anticancer activity of Acanthus ilicifolius extracted from the mangroves forest of Karwar, West coast of India. 2011; Available from: https://agris.fao.org/agris-search/search.do?recordID=AV2012067062

3. Palaniyandi T, Sivaji A, Thiruganasambandam R, Natarajan S, Hari R, Others. In Vitro antigastric cancer activity of squalene, a triterpenoid compound isolated from Rhizophora

Mucronata mangrove plant leaves against AGS cell line. Pharmacogn Mag [Internet]. 2018;14(57):369. Available from: https://www.phcog.com/article.asp?issn=0973-1296;year=2018;volume=14;issue=57;spage=369;epage=376;aulast=Palaniyandi

4. Bandaranayake WM. Bioactivities, bioactive compounds and chemical constituents of mangrove plants. Wetlands Ecol Manage [Internet]. 2002 Dec 1;10(6):421–52. Available from: https://doi.org/10.1023/A:1021397624349

5. Chater KF, Hopwood DA. Streptomyces [Internet]. Bacillus subtilis and Other Gram-Positive Bacteria. 2014. p. 83–99. Available from: http://dx.doi.org/10.1128/9781555818388.ch6

6. Hopwood DA, Hopwood of GD. Streptomyces in Nature and Medicine: The Antibiotic Makers [Internet]. Oxford University Press, USA; 2007. 250 p. Available from: https://play.google.com/store/books/details?id=zPURDAAAQBAJ

7. Pa J. Baylin SB. The epigenomics of cancer. Cell. 2007;128(4):683–92.

8. Chu E, Sartorelli AC. Cancer chemotherapy. Basic Clin Pharmacol Toxicol [Internet]. 2004;9:898–930. Available from: https://www.academia.edu/download/58380558/Katzung_-_Basic_and_Clinical_Pharmacology_14th_Edition_c2018_txtbk.pdf#page=962

9. Lira-Medeiros CF, Parisod C, Fernandes RA, Mata CS, Cardoso MA, Ferreira PCG. Epigenetic variation in mangrove plants occurring in contrasting natural environment. PLoS One [Internet]. 2010 Apr 26;5(4):e10326. Available from: http://dx.doi.org/10.1371/journal.pone.0010326

10. Neve RM, Chin K, Fridlyand J, Yeh J, Baehner FL, Fevr T, et al. A collection of breast cancer cell lines for the study of functionally distinct cancer subtypes. Cancer Cell [Internet]. 2006 Dec;10(6):515–27. Available from: http://dx.doi.org/10.1016/j.ccr.2006.10.008

11. Rajeshkumar S, Kumar SV, Ramaiah A, Agarwal H, Lakshmi T, Roopan SM. Biosynthesis of zinc oxide nanoparticles usingMangifera indica leaves and evaluation of their antioxidant and cytotoxic properties in lung cancer (A549) cells. Enzyme Microb Technol [Internet]. 2018 Oct;117:91–5. Available from: http://dx.doi.org/10.1016/j.enzmictec.2018.06.009

12. Nandhini NT, Rajeshkumar S, Mythili S. The possible mechanism of eco-friendly synthesized nanoparticles on hazardous dyes degradation. Biocatal Agric Biotechnol [Internet]. 2019 May 1;19:101138. Available from: https://www.sciencedirect.com/science/article/pii/S1878818118308235

13. Vairavel M, Devaraj E, Shanmugam R. An eco-friendly synthesis of Enterococcus sp.–mediated gold nanoparticle induces cytotoxicity in human colorectal cancer cells. Environ Sci Pollut Res [Internet]. 2020 Mar 1;27(8):8166–75. Available from: https://doi.org/10.1007/s11356-019-07511-x

UNDER PEER REVIEW

14. Gomathi M, Prakasam A, Rajkumar PV, Rajeshkumar S, Chandrasekaran R, Anbarasan PM. Green synthesis of silver nanoparticles using Gymnema sylvestre leaf extract and evaluation of its antibacterial activity [Internet]. Vol. 32, South African Journal of Chemical Engineering. 2020. p. 1–4. Available from: http://dx.doi.org/10.1016/j.sajce.2019.11.005

15. Rajasekaran S, Damodharan D, Gopal K, Rajesh Kumar B, De Poures MV. Collective influence of 1-decanol addition, injection pressure and EGR on diesel engine characteristics fueled with diesel/LDPE oil blends. Fuel [Internet]. 2020 Oct 1;277:118166. Available from: https://www.sciencedirect.com/science/article/pii/S0016236120311625

16. Santhoshkumar J, Sowmya B, Venkat Kumar S, Rajeshkumar S. Toxicology evaluation and antidermatophytic activity of silver nanoparticles synthesized using leaf extract of Passiflora caerulea. S Afr J Chem Eng [Internet]. 2019 Jul;29:17–23. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1026918519300253

17. Raj R K, D E, S R. β-Sitosterol-assisted silver nanoparticles activates Nrf2 and triggers mitochondrial apoptosis via oxidative stress in human hepatocellular cancer cell line. J Biomed Mater Res A [Internet]. 2020 Sep;108(9):1899–908. Available from: http://dx.doi.org/10.1002/jbm.a.36953

18. Saravanan M, Arokiyaraj S, Lakshmi T, Pugazhendhi A. Synthesis of silver nanoparticles from Phenerochaete chrysosporium (MTCC-787) and their antibacterial activity against human pathogenic bacteria. Microb Pathog [Internet]. 2018 Apr;117:68–72. Available from: http://dx.doi.org/10.1016/j.micpath.2018.02.008

19. Gheena S, Ezhilarasan D. Syringic acid triggers reactive oxygen species–mediated cytotoxicity in HepG2 cells. Hum Exp Toxicol [Internet]. 2019 Jun 1;38(6):694–702. Available from: https://doi.org/10.1177/0960327119839173

20. Ezhilarasan D, Sokal E, Najimi M. Hepatic fibrosis: It is time to go with hepatic stellate cell-specific therapeutic targets. Hepatobiliary Pancreat Dis Int [Internet]. 2018 Jun;17(3):192–7. Available from: http://dx.doi.org/10.1016/j.hbpd.2018.04.003

21. Ezhilarasan D. Oxidative stress is bane in chronic liver diseases: Clinical and experimental perspective. Arab J Gastroenterol [Internet]. 2018 Jun;19(2):56–64. Available from: http://dx.doi.org/10.1016/j.ajg.2018.03.002

22. Gomathi AC, Xavier Rajarathinam SR, Mohammed Sadiq A, Rajeshkumar S. Anticancer activity of silver nanoparticles synthesized using aqueous fruit shell extract of Tamarindus indica on MCF-7 human breast cancer cell line. J Drug Deliv Sci Technol [Internet]. 2020 Feb 1;55:101376. Available from: https://www.sciencedirect.com/science/article/pii/S1773224719313693

23. Dua K, Wadhwa R, Singhvi G, Rapalli V, Shukla SD, Shastri MD, et al. The potential of siRNA based drug delivery in respiratory disorders: Recent advances and progress. Drug Dev Res [Internet]. 2019 Sep;80(6):714–30. Available from: http://dx.doi.org/10.1002/ddr.21571

UNDER PEER REVIEW

24. Ramesh A, Varghese S, Jayakumar ND, Malaiappan S. Comparative estimation of sulfiredoxin levels between chronic periodontitis and healthy patients - A case-control study. J Periodontol [Internet]. 2018 Oct;89(10):1241–8. Available from: http://dx.doi.org/10.1002/JPER.17-0445

25. Arumugam P, George R, Jayaseelan VP. Aberrations of m6A regulators are associated with tumorigenesis and metastasis in head and neck squamous cell carcinoma. Arch Oral Biol [Internet]. 2021 Feb;122:105030. Available from: http://dx.doi.org/10.1016/j.archoralbio.2020.105030

26. Joseph B, Prasanth CS. Is photodynamic therapy a viable antiviral weapon against COVID-19 in dentistry? Oral Surg Oral Med Oral Pathol Oral Radiol [Internet]. 2021 Jul;132(1):118–9. Available from: http://dx.doi.org/10.1016/j.oooo.2021.01.025

27. Ezhilarasan D, Apoorva VS, Ashok VN. Syzygium cumini extract induced reactive oxygen species-mediated apoptosis in human oral squamous carcinoma cells. J Oral Pathol Med [Internet]. 2019 Feb [cited 2021 Sep 15];48(2). Available from: https://pubmed.ncbi.nlm.nih.gov/30451321/

28. Duraisamy R, Krishnan CS, Ramasubramanian H, Sampathkumar J, Mariappan S, Navarasampatti Sivaprakasam A. Compatibility of Nonoriginal Abutments With Implants: Evaluation of Microgap at the Implant-Abutment Interface, With Original and Nonoriginal Abutments. Implant Dent [Internet]. 2019 Jun;28(3):289–95. Available from: http://dx.doi.org/10.1097/ID.0000000000000885

29. Gnanavel V, Roopan SM, Rajeshkumar S. Aquaculture: An overview of chemical ecology of seaweeds (food species) in natural products. Aquaculture [Internet]. 2019 May 30;507:1–6. Available from: https://www.sciencedirect.com/science/article/pii/S0044848618328072

30. Markov A, Thangavelu L, Aravindhan S, Zekiy AO, Jarahian M, Chartrand MS, et al. Mesenchymal stem/stromal cells as a valuable source for the treatment of immune-mediated disorders. Stem Cell Res Ther [Internet]. 2021 Mar 18;12(1):192. Available from: http://dx.doi.org/10.1186/s13287-021-02265-1

31. Danda AK, Krishna TM, Narayanan V, Siddareddi A. Influence of primary and secondary closure of surgical wound after impacted mandibular third molar removal on postoperative pain and swelling--a comparative and split mouth study. J Oral Maxillofac Surg [Internet]. 2010 Feb [cited 2021 Sep 15];68(2). Available from: https://pubmed.ncbi.nlm.nih.gov/20116700/

32. Ramadurai N, Gurunathan D, Samuel AV, Subramanian E, Rodrigues SJL. Effectiveness of 2% Articaine as an anesthetic agent in children: randomized controlled trial. Clin Oral Investig [Internet]. 2019 Sep [cited 2021 Sep 15];23(9). Available from: https://pubmed.ncbi.nlm.nih.gov/30552590/

33. Sathivel A, Raghavendran HR, Srinivasan P, Devaki T. Anti-peroxidative and anti-hyperlipidemic nature of Ulva lactuca crude polysaccharide on D-galactosamine induced hepatitis in rats. Food Chem Toxicol [Internet]. 2008 Oct [cited 2021 Sep 15];46(10).

UNDER PEER REVIEW

Available from: https://pubmed.ncbi.nlm.nih.gov/18706469/

34. Panda S, Doraiswamy J, Malaiappan S, Varghese SS, Del Fabbro M. Additive effect of autologous platelet concentrates in treatment of intrabony defects: a systematic review and meta-analysis. J Investig Clin Dent [Internet]. 2016 Feb [cited 2021 Sep 15];7(1). Available from: https://pubmed.ncbi.nlm.nih.gov/25048153/

35. Neelakantan P, Varughese AA, Sharma S, Subbarao CV, Zehnder M, De-Deus G. Continuous chelation irrigation improves the adhesion of epoxy resin-based root canal sealer to root dentine. Int Endod J [Internet]. 2012 Dec [cited 2021 Sep 15];45(12). Available from: https://pubmed.ncbi.nlm.nih.gov/22612994/

36. Govindaraju L, Neelakantan P, Gutmann JL. Effect of root canal irrigating solutions on the compressive strength of tricalcium silicate cements. Clin Oral Investig [Internet]. 2017 Mar [cited 2021 Sep 15];21(2). Available from: https://pubmed.ncbi.nlm.nih.gov/27469101/

37. Sekhar CH, Narayanan V, Baig MF. Role of antimicrobials in third molar surgery: prospective, double blind,randomized, placebo-controlled clinical study. Br J Oral Maxillofac Surg [Internet]. 2001 Apr [cited 2021 Sep 15];39(2). Available from: https://pubmed.ncbi.nlm.nih.gov/11286448/

38. DeSouza SI, Rashmi MR, Vasanthi AP, Joseph SM, Rodrigues R. Mobile phones: the next step towards healthcare delivery in rural India? PLoS One [Internet]. 2014 Aug 18 [cited 2021 Sep 15];9(8). Available from: https://pubmed.ncbi.nlm.nih.gov/25133610/

39. Nasim I, Neelakantan P, Sujeer R, Subbarao CV. Color stability of microfilled, microhybrid and nanocomposite resins--an in vitro study. J Dent [Internet]. 2010 [cited 2021 Sep 15];38 Suppl 2. Available from: https://pubmed.ncbi.nlm.nih.gov/20553993/

40. Danda AK, Muthusekhar MR, Narayanan V, Baig MF, Siddareddi A. Open versus closed treatment of unilateral subcondylar and condylar neck fractures: a prospective, randomized clinical study. J Oral Maxillofac Surg [Internet]. 2010 Jun [cited 2021 Sep 15];68(6). Available from: https://pubmed.ncbi.nlm.nih.gov/20303209/

41. Molecular structure and vibrational spectra of 2,6-bis(benzylidene)cyclohexanone: A density functional theoretical study. Spectrochim Acta A Mol Biomol Spectrosc [Internet]. 2011 Jan 1 [cited 2021 Sep 15];78(1):113–21. Available from: http://dx.doi.org/10.1016/j.saa.2010.09.007

42. Putchala MC, Ramani P, Herald J. Sherlin, Premkumar P, Natesan A. Ascorbic acid and its pro-oxidant activity as a therapy for tumours of oral cavity – A systematic review [Internet]. Vol. 58, Archives of Oral Biology. 2013. p. 563–74. Available from: http://dx.doi.org/10.1016/j.archoralbio.2013.01.016

43. Neelakantan P, Grotra D, Sharma S. Retreatability of 2 mineral trioxide aggregate-based root canal sealers: a cone-beam computed tomography analysis. J Endod [Internet]. 2013 Jul;39(7):893–6. Available from: http://dx.doi.org/10.1016/j.joen.2013.04.022

UNDER PEER REVIEW

44. Suresh P, Marimuthu K, Ranganathan S, Rajmohan T. Optimization of machining parameters in turning of Al-SiC-Gr hybrid metal matrix composites using grey-fuzzy algorithm [Internet]. Vol. 24, Transactions of Nonferrous Metals Society of China. 2014. p. 2805–14. Available from: http://dx.doi.org/10.1016/s1003-6326(14)63412-9

31. Khalifa ,S. A. M. Nizar Elias, Mohamed A. Farag, Lei Chen, Aamer Saeed et al., 2019. Marine Natural Products: A Source of Novel Anticancer Drugs, Mar Drugs. 17(9): 491. doi: 10.3390/md17090491

32. Genilloud O, 2017. Actinomycetes: still a source of novel antibiotics. Nat Prod Rep. 34(10):1203-1232.

33. Huang C, Leung RK, Guo M, Tuo L, Guo L, Yew WW, Lou I, Lee SMY, Sun C, 2016. Genome-guided Investigation of Antibiotic Substances produced by Allosalinactinospora lopnorensis CA15-2(T) from Lop Nor region, China. Sci Rep. 6():20667.

34. Isnansetyo A, Kamei Y, 2009. Bioactive substances produced by marine isolates of Pseudomonas. J Ind Microbiol Biotechnol. 36(10):1239-48.

35. Sithranga Boopathy N., Kathiresan K. Anticancer drugs from marine flora: An overview. J. Oncol. 2010;**2010**:18. doi: 10.1155/2010/214186.

36. Malaker A., Ahmad S.A.I. Therapeutic potency of anticancer peptides derived from marine organism. Int. J. Eng. 2013;**2**:2305–8269.

37. Cho JY, Williams PG, Kwon HC, Jensen PR, Fenical W, 2007. Lucentamycins A-D, cytotoxic peptides from the marine-derived actinomycete Nocardiopsis lucentensis. J Nat Prod. 70(8):1321-8.

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