ANTI-INFLAMMATORY AND ANTIOXIDANT ACTIVITY OF WHITE PEPPER OLEORESIN MEDIATED SELENIUM NANOPARTICLES

Running title: Activity of white pepper oleoresin mediated selenium nanoparticles

ABSTRACT:

Introduction: Indian spices such as turmeric, ginger, and mint bring color and flavor to food and cure many ailments too.

Aim: To study the anti-inflammatory and antioxidant activity of white pepper oleoresin-mediated selenium nanoparticles.

Materials and Method: The white pepper oleoresin extract is collected from Synthetic Industries, with a product code - 4010000835. Selenium nanoparticles were initially prepared using white pepper oleoresin and DPPH assay was performed on the different concentrations of white pepper oleoresin (10, 20, 30, 40, 50 µg/ml) for antioxidant activity, and anti-inflammatory activity was tested by the following convention proposed by Muzushima and Kabayashi with specific alterations.

Results: White pepper has shown a very good anti-inflammatory effect and antioxidant activity when compared to the standard used at higher concentrations. Selenium nanoparticles appeared to have 90 percent inhibition in 50µL, which was also higher than the standard. In addition , they seemed to have 85 percent inhibition in 50µL, which was also lower than the standard.

Conclusion: The present study has demonstrated an eco-friendly and cost-effective synthesis of Selenium nanoparticles using White pepper oleoresin. White pepper oleoresin mediated Selenium nanoparticles were with good anti-inflammatory and antioxidant activity which may be utilized include for its use as an inflammatory and antioxidant agents.

Keywords: Anti-inflammatory activity; Antioxidant activity; white pepper oleoresin; selenium nanoparticle, environment friendly, green synthesis

Comment [I1]: Change to

Comment [I2]: By using?

Comment [I3]: During…month and …year?

Comment [I4]: Change to

INTRODUCTION:

Comment [I5]: Please, you can reduce this part

Nanoparticle, an ultrafine unit with dimensions measured in nanometres (1). Due to their submicroscopic scale hasic material characteristics, and engineered nanoparticles can find functional applications in several fields, including medicine, engineering, catalysis, and environmental remediation (2). A nanoparticle is a microscopic particle between 1 and 100 nanometres in size (3).

Comment [I6]: Nanometers

Comment [I7]: Basic

Comment [I8]: Nanometers

White pepper contains the seed of the pepper plant on its own and the darker-colored skin of the pepper fruit is separated. This is normally achieved by a method known as retting, where red pepper berries, which are entirely mature, are immersed in water for about a week, after which the pepper's flesh softens and decomposes (4). White pepper is also used in cream sauces, Chinese and Thai dishes, and salads. White Pepper Oleoresin (5) is produced by solvent extraction of the decorticated, ground dried berries of *Piper nigrum L*. The scent of the product is typical of white pepper, with a clear caustic note and pungency behind it. Its taste is initially mildly warm and friendly, accompanied by a pungent, biting feeling (6).

Comment [I9]: Ratio?

Inflammation, which is a pattern of response to injury, involves the accumulation of cells and exudates in irritated tissues, which allows protection from further damage. Inflammation has been investigated for thousands of years to counteract its impact on the body. In AD 30, Cel-is described the 4 classic signs of inflammation (rubor, calor, dolor, and tumor, or redness, heat, pain, and the inflammatory) basis of the disease becomes clear, anti-inflammatory food and food products become of greater interest (7). The role of oxidation in the body and food has been generally recognized. Oxidative metabolism is important for cell survival. A side effect of this dependency is the development of free radicals and other reactive oxygen species which cause oxidative changes. There is growing evidence of the presence of such organisms in several natural in vivo regulatory systems (8). When excess free radicals are produced, they will bypass defensive enzymes such as superoxide dismutase, catalase, and peroxidase and trigger destructive and lethal cellular effects (e.g. apoptosis) by oxidizing membrane lipids, cellular

Comment [I10]: ?

proteins, DNA, and enzymes, thereby shutting down cellular respiration. Besides, reactive oxygen species seem to affect cell signaling processes in currently unraveled ways (9). Oxidation can also affect food, where it is one of the main causes of chemical spoilage, resulting in rancidity and/or degradation in the nutritional consistency, color, taste, texture, and protection of food. It is predicted that half of the world's fruit and vegetable crops are lost due to deteriorating post-harvest reactions. Defense mechanisms against the effects of excessive oxidation are given by the action of different antioxidants and the need to quantify antioxidant activity is well documented (10).

Methods for evaluating antioxidant behavior fell into two broad categories representing the emphasis on food activity or human bioactivity. In the case of food systems, it is essential to determine the effectiveness of the antioxidant(s) in providing food protection against oxidative spoilage. The subcategory includes measuring food activity, in particular fruit, vegetables, and drinks, but to predict dietary pressure and in vivo activity. Oxidative stress in humans is caused by imbalances in antioxidant status (reactive oxygen species versus defense and repair mechanisms). Enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, plus vitamin E, uric acid, and serum albumins, are among the endogenous defenses. In addition to these defenses, the intake of dietary antioxidants is also essential. The lack of a single, definable substrate in several instances in vivo is a significant difference from food-based systems (11).

The antioxidant agent may be defined as 'any material that significantly slows or prevents oxidation of the substrate when present at low concentrations compared to those of the oxidizing substrate.' For simplicity, antioxidants have historically been classified into two groups, primary or chain-breaking antioxidants, and secondary or preventive antioxidants (12). Secondary or preventive antioxidants are substances that slow down the oxidation rate. This can be done in various ways, including reducing or singlet oxygen. Primary antioxidants, AH, when present in trace quantities, can either postpone or inhibit the initiation of lipid radical reactions or inhibit the spread by reacting with peroxyl or alkoxyl radicals (13).

Comment [I11]: Add

Comment [I12]: Full name

Previously, our team had conducted numerous studies on oleoresins and nanoparticles, (14) - (15,16), gold nanoparticles(17),(18), and other nanoparticles (19) - (20). Our team has extensive knowledge and research experience that has translated into high quality publications(21–25) (26)(27)(28)(29)(30)(31)(32)(33)(34)(35)(36)(37)(38)(38,39)(40)(40,41)(42)(43)

The aim of the present study was to evaluate the anti-inflammatory and antioxidant activity of white pepper oleoresin-mediated selenium nanoparticles.

MATERIALS AND METHODS:

Study setting: The study was conducted in the Nanomedicine laboratory, Dept. of Pharmacology, Saveetha Dental College after obtaining approval from the Scientific Review Board (IHEC/SDC/UG-1921/21/130)

Preparation of plant:

The white pepper oleoresin extract was collected from Synthite Industries Pvt Limited, Kerala, with a product code - 4010000835. The preparation was obtained by solvent extraction of the white pepper prepared from ripe pepper berries by the disintegration of the skin, decortication, and drying. It contains a volatile oil in a composition of about 23 - 25 ml/100g.

Synthesis of selenium nanoparticles:

Selenium nanoparticles were synthesized using white pepper oleoresin by adding 0.2 mL of white pepper oleoresin to 100 mL of distilled water, 20 millimolar of sodium selenite was added and kept in an orbital shaker. The nanoparticles were then centrifuged with the aid of a Lark refrigerator centrifuge at 8000 rpm for 10 minutes. The pellets were then separated from the supernatant and transferred into an Eppendorf tube. The color changes were observed at different periods by a double-beam UV-Vis spectrophotometer at wavelengths ranging from 250 nm to 750 nm. The selenium nanoparticles~~, thus~~ obtained were purified by repeated centrifugation at 8000 rpm for 10 minutes. The pellet was collected in a cuvette and the peak value was measured.

Anti-inflammatory activity:

The anti-inflammatory activity for white pepper oleoresin-mediated selenium nanoparticles was tested by the following convention proposed by Muzushima and Kabayashi with specific alterations (44). 0.05 mL of white pepper oleoresin of various fixations (10µL, 20µL, 30µL, 40µL, 50µL) was added to 0.45 mL bovine serum albumin (1% aqueous solution) and the pH of the mixture was acclimated to 6.3 utilizing a modest quantity of 1N hydrochloric acid. These samples were incubated at room temperature at 55 °C for 20 min and then heated in a water bath

Comment [I13]: You can write the conclusions obtained from these studies and you don't use it in the discussion

Comment [I14]: Temperature and time

Comment [I15]: Yield%?

Comment [I16]: Change to

Comment [I17]: Change to

Comment [I18]: Delete

Comment [I19]: Change to

for 30 min. The samples were cooled and the absorbance was estimated spectrophotometrically at 660 nm. Diclofenac Sodium was used as the standard. DMSO is utilized as a control (45).

Comment [I20]: Full name

Percentage of protein denaturation was determined utilizing the following equation,

$$\% \text{ inhibition} = \frac{\text{Absorbance of control} - \text{Absorbance of sample} \times 100}{\text{Absorbance of control}}$$

Comment [I21]: --------------------

Antioxidant activity:

Comment [I22]: Reference

Comment [I23]: Full name

DPPH assay was used to test the antioxidant activity of selenium nanoparticles. Diverse concentrations (2-10 µg/ml) of white pepper oleoresin interceded selenium nanoparticle was mixed with 1 ml of 0.1 mM DPPH in methanol and 450 µl of 50 mM Tris HCl buffer (pH 7.4) and incubated for 30 minutes. Later, the reduction in the quantity of DPPH free radicals was assessed dependent on the absorbance at 517 nm. BHT was employed as control. The percentage of inhibition was determined from the following equation,

$$\% \text{ inhibition} = \frac{\text{Absorbance of control} - \text{Absorbance of test sample} \times 100}{\text{Absorbance of control}}$$

Comment [I24]: -----------------------

Comment [I25]: Statistical analysis

RESULTS AND DISCUSSION:

Comment [I26]: Needs to more studies

White pepper is considered to possess a good anti-inflammatory and antioxidant activity effect at higher concentrations (50µL) and when compared to the standard used. Over the most recent years, research on medicinal, antimutagenic, antioxidant, and anticarcinogenic properties of spices has been conducted. In this study, the anti-inflammatory and antioxidant activity was conducted by convention proposed by Muzushima and Kabayashi with specific alterations and DPPH assay respectively.

Comment [I27]: Delete

Comment [I28]: Were

Visual Identification

The color changes in the reaction mixture were observed at various intervals of incubation time. The sodium Selenite is reduced into selenium nanoparticles and it is identified by color change (Figure 1). The color changed from light yellow to cream viscous liquid indicating the formation of selenium nanoparticles. The intensity of viscous liquid rises with an increase in incubation

Comment [I29]: ?

time. After 28hr cream viscous liquid was observed, no color change was seen, which indicated that synthesis of selenium nanoparticles was completed.

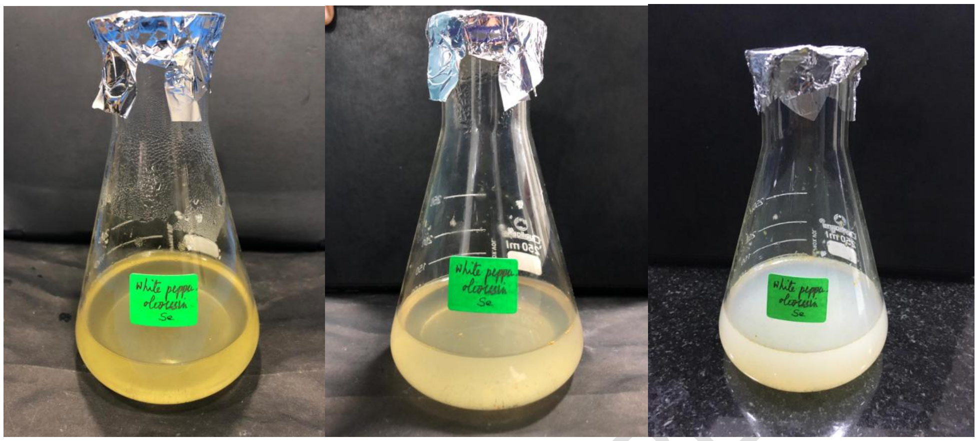

Figure 1: Visual observation of color changes at various periods of incubation time indicating the reduction of selenite ions to selenium nanoparticles.

A:….., B:….. and C:……

Comment [I30]: Write

UV-Visible absorption spectrophotometer activity:

UV-Visible analysis depends on the color in the reaction. This occurs due to the excitation of the surface plasmon resonance band in a reaction mixture at different wavelength regions from 250 nm to 750 nm and was observed at various time intervals. Figure 2 shows the UV absorption spectra of the synthesized selenium nanoparticles using white pepper oleoresin. With an increase in incubation time, the spectrum clearly shows that the absorbance steadily increases. The plasmon resonance band for selenium nanoparticles was peak positioned at 350 nm. The iron nanoparticles synthesized using an aqueous *Musa ornate* flower have been shown to produce a maximum absorption peak around 310 nm (46).

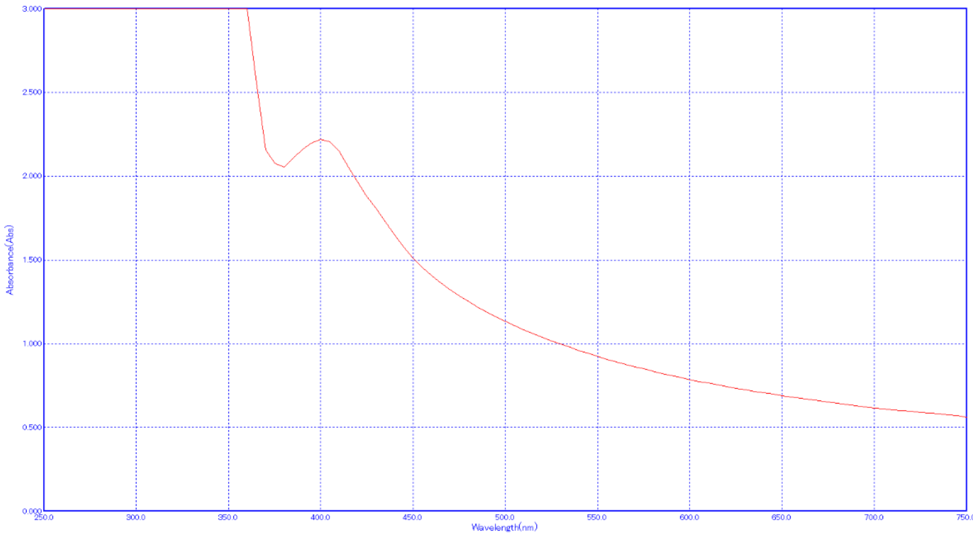

Figure 2: UV- Visible spectrophotometer analysis of White pepper oleoresin mediated selenium nanoparticles recorded as a function of time ('X-axis' represents 'Absorbance' [Abs] and Y-axis represents 'Wavelength' [nm]).

Anti-inflammatory activity:

The anti-inflammatory activity for white pepper oleoresin-mediated selenium nanoparticles was tested by the following convention proposed by Muzushima and Kabayashi with specific alterations (Pratik Das et al.,2019). The various fixations (47) of white pepper oleoresin from 10µL-50µL obtained various results in comparison to the standard Diclofenac sodium. In 10µL, selenium nanoparticles appeared to have 25% inhibition which was lower than the standard. In 20µL, the nanoparticle showed 55% inhibition which was more or less similar to the standard. In 30µL, selenium nanoparticles appeared to have 65% inhibition which was also similar to the standard. In 40µL, the nanoparticle showed 80% inhibition which was higher than the standard. In 50µL, selenium nanoparticles appeared to have 90% inhibition which was also higher than the standard. As a result, when the concentration of the selenium nanoparticles increased, the inflammatory activity also increased.

Comment [I31]: No. or names

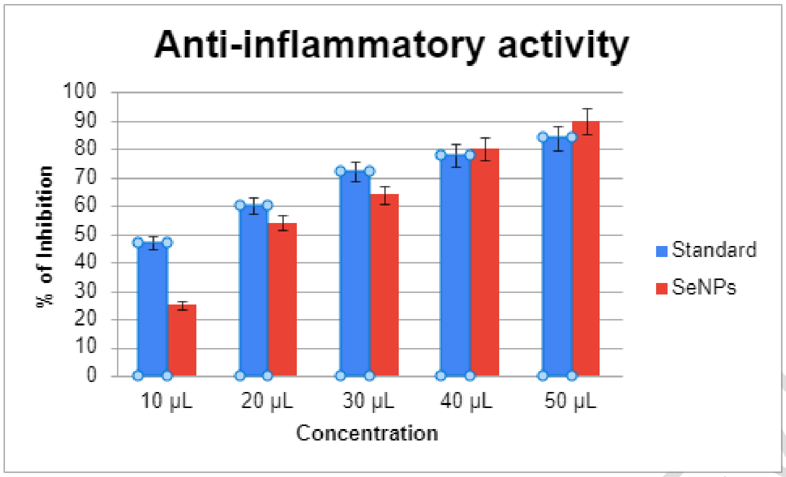

Figure 3: Anti-inflammatory activity at various concentrations from 10µL-50µL and the percentage of inhibition. The X-axis shows the concentration of the nanoparticle and the Y-axis shows the percentage inhibition. Values are done in triplicate n= 3, Mean +/_ SD.

Antioxidant activity:

The antioxidant activity for white pepper oleoresin-mediated selenium nanoparticles was tested by DPPH Assay . The various fixations of white pepper oleoresin from 10µL-50µL obtained various results in comparison to the standard control BHT. In 10µL, selenium nanoparticles appeared to have 60% inhibition which was lower than the standard. In 20µL, the nanoparticle showed 65% inhibition which was significantly lower than the standard. In 30µL, selenium nanoparticles appeared to have 70% inhibition which was also lower than the standard. In 40µL, the nanoparticle showed 80% inhibition which was lower but the range was near the standard. In 50µL, selenium nanoparticles appeared to have 85% inhibition which was also lower than the standard whereas it increased and reached the standard. As a result, when the concentration of the selenium nanoparticles was raised, the antioxidant activity also increased.

The limitation of the study was that the activity was evaluated only by *in vitro* techniques and can be extended in animal models in the future.

Comment [I32]: Add fig. 4

Comment [I33]: Full name

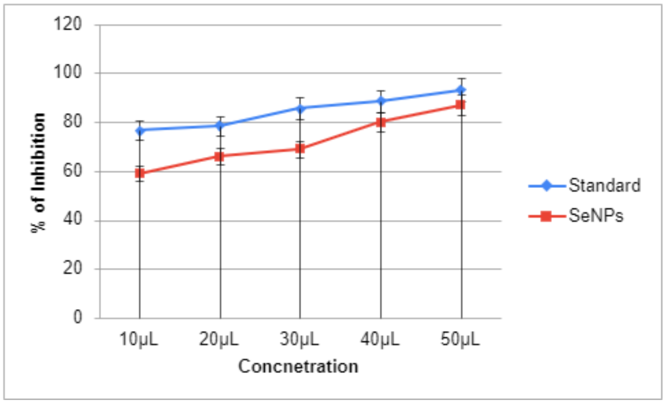

Figure 4: Antioxidant activity at various concentrations from 10µL-50µL and the percentage of inhibition. The X-axis shows the concentration of the nanoparticle and the Y-axis shows the percentage inhibition. Values are done in triplicate n= 3, Mean +/_ SD.

CONCLUSION:

The present study has demonstrated an eco-friendly and cost-effective synthesis of Selenium nanoparticles using White pepper oleoresin (48-57). The white pepper oleoresin-mediated selenium nanoparticles are good anti-inflammatory and antioxidant activity at higher concentrations based on the results obtained. White pepper is a natural product with its strong aroma and good properties that can be used in treating inflammation and can be used to prevent oxidation and prevent the detrimental effects of other medications. Further invasive studies can support its use in the future.

Comment [I34]: Change to

Comment [I35]: Add

REFERENCES:

Comment [I36]: Follow the journal format and you can reduce it

1. Schmid G. Nanoparticles: From Theory to Application. John Wiley & Sons; 2006. 444 p.

2. Chung EJ, Leon L, Rinaldi C. Nanoparticles for Biomedical Applications: Fundamental Concepts, Biological Interactions and Clinical Applications. Elsevier; 2019. 440 p.

3. Shukla AK, Iravani S. Green Synthesis, Characterization and Applications of Nanoparticles. Elsevier; 2018. 548 p.

4. Vinod V, Kumar A, Zachariah TJ. Isolation, characterization and identification of pericarp-degrading bacteria for the production of off-odour-free white pepper from fresh berries of Piper nigrum L. J Appl Microbiol. 2014 Apr;116(4):890–902.

5. Paul RP, Roy A, M MA, Shanmugam R. Antibacterial Activity of White Pepper Oleoresin Mediated Silver Nanoparticles against Oral Pathogens [Internet]. Vol. 9, Journal of Evolution of Medical and Dental Sciences. 2020. p. 2352–5. Available from: http://dx.doi.org/10.14260/jemds/2020/510

6. Schulz H, Baranska M, Quilitzsch R, Schütze W, Lösing G. Characterization of peppercorn, pepper oil, and pepper oleoresin by vibrational spectroscopy methods. J Agric Food Chem. 2005 May 4;53(9):3358–63.

7. Chatterjee S, Jungraithmayr W, Bagchi D. Immunity and Inflammation in Health and Disease: Emerging Roles of Nutraceuticals and Functional Foods in Immune Support. Academic Press; 2017. 476 p.

8. Zorov DB, Andrianova NV, Babenko VA, Bakeeva LE, Zorov SD, Zorova LD, et al. Nonphosphorylating Oxidation in Mitochondria and Related Processes. Biochemistry . 2020 Dec;85(12):1570–7.

9. Frankel EN. Lipid Oxidation. Elsevier; 2014. 488 p.

10. Decker EA, Elias RJ, Julian McClements D. Oxidation in Foods and Beverages and Antioxidant Applications: Management in Different Industry Sectors. Elsevier; 2010. 552 p.

11. Packer L, Hiramatsu M, Yoshikawa T. Antioxidant Food Supplements in Human Health. Elsevier; 1999. 511 p.

12. Frankel EN. Antioxidants in Food and Biology: Facts and Fiction. Woodhead Pub Limited; 2007. 254 p.

13. Ahmad R. Free Radicals, Antioxidants and Diseases. BoD – Books on Demand; 2018. 148 p.

14. Jain A, Anitha R, Rajeshkumar S. Anti inflammatory activity of Silver nanoparticles synthesised using Cumin oil [Internet]. Vol. 12, Research Journal of Pharmacy and Technology. 2019. p. 2790. Available from: http://dx.doi.org/10.5958/0974-360x.2019.00469.4

15. Rajeshkumar S, Bharath LV. Mechanism of plant-mediated synthesis of silver nanoparticles – A review on biomolecules involved, characterisation and antibacterial activity [Internet]. Vol. 273, Chemico-Biological Interactions. 2017. p. 219–27. Available from: http://dx.doi.org/10.1016/j.cbi.2017.06.019

16. Jeevitha M, Rajeshkumar S. Antimicrobial Activity of Silver Nanoparticles Synthesized Using Marine Brown Seaweed Spatoglossum Asperum Against Oral Pathogens [Internet]. Vol. 10, Indian Journal of Public Health Research & Development. 2019. p. 3568.

Available from: http://dx.doi.org/10.5958/0976-5506.2019.04140.8

17. Santhoshkumar J, Rajeshkumar S, Venkat Kumar S. Phyto-assisted synthesis, characterization and applications of gold nanoparticles - A review. Biochem Biophys Rep. 2017 Sep;11:46–57.

18. Menon S, S. R, S. VK. A review on biogenic synthesis of gold nanoparticles, characterization, and its applications [Internet]. Vol. 3, Resource-Efficient Technologies. 2017. p. 516–27. Available from: http://dx.doi.org/10.1016/j.reffit.2017.08.002

19. Agarwal H, Venkat Kumar S, Rajeshkumar S. A review on green synthesis of zinc oxide nanoparticles – An eco-friendly approach [Internet]. Vol. 3, Resource-Efficient Technologies. 2017. p. 406–13. Available from: http://dx.doi.org/10.1016/j.reffit.2017.03.002

20. Agarwal H, Menon S, Venkat Kumar S, Rajeshkumar S. Mechanistic study on antibacterial action of zinc oxide nanoparticles synthesized using green route [Internet]. Vol. 286, Chemico-Biological Interactions. 2018. p. 60–70. Available from: http://dx.doi.org/10.1016/j.cbi.2018.03.008

21. 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. 2018 Oct;117:91–5.

22. Nandhini NT, Rajeshkumar S, Mythili S. The possible mechanism of eco-friendly synthesized nanoparticles on hazardous dyes degradation. Biocatal Agric Biotechnol. 2019 May 1;19:101138.

23. 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. 2020 Mar 1;27(8):8166–75.

24. 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

25. 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. 2020 Oct 1;277:118166.

26. Veerasamy R, Roy A, Karunakaran R, Rajak H. Structure-Activity Relationship Analysis of Benzimidazoles as Emerging Anti-Inflammatory Agents: An Overview. Pharmaceuticals [Internet]. 2021 Jul 11;14(7). Available from: http://dx.doi.org/10.3390/ph14070663

27. Dhayanithi J, Rajeshkumar S, Roy A, Lakshmi T. Preparation and Evaluation of Antifungal Activity of Arrow Root Mediated Selenium Nanoparticles Against Candida Albicans -.

Journal of Complementary Medicine Research. 2020;11(5):83–8.

28. Blessy PS, Rajeshkumar S, Lakshmi T, Roy A. Enhanced Antibacterial Activity of Arrowroot Mediated Selenium Nanoparticles Against Streptococcus Mutans And Lactobacillus Species -. Journal of Complementary Medicine Research. 2020;11(5):17–23.

29. Lakshmi T, Roy A, Raghunandhakumar S, Merlin ARS. Invitro Cytotoxicity Assay of Acacia Catechu Ethanolic Seed Extract Using Brine Shrimp -. Journal of Complementary Medicine Research. 2020;11(5):89–92.

30. R. V Geetha TL. In vitro evaluation of antimicrobial activity and estimation of Epicatechin from the fruit extract of Prunus armeniaca L using HPTLC technique -. Journal of Complementary Medicine Research. 2020;11(5):113–22.

31. Assessment of Oxidative Stress and Antioxidant Levels in Chronic Periodontitis Patients [Internet]. [cited 2021 Aug 31]. Available from: http://alinteridergisi.com/article/assessment-of-oxidative-stress-and-antioxidant-levels-in-chronic-periodontitis-patients/

32. Dharahaas C, Lakshmi T, Roy A, Raghunandhakumar S. Genotoxicity potentials of methanolic extracts of Mimosa pudica against oral cancer cells. Journal of Complementary Medicine Research. 2020;11(5):24–9.

33. Lakshmi T, Roy A, George RS, Raghunandhakumar S. Antibacterial Activity of Acacia Catechu Seed Against Urinary Tract Pathogens. Journal of Complementary Medicine Research. 2020;11(5):123–7.

34. Jai Rexlin PE, Roy A, Rajeshkumar S, Lakshmi T. Antimicrobial Activity of Coriander Oleoresin Mediated Selenium Nanoparticles Against Oral Pathogens. -. Journal of Complementary Medicine Research. 2020;11(5):35–40.

35. Lakshmi T, Ramasamy R, Thirumalaikumaran R. Preliminary Phytochemical analysis and In vitro Antioxidant, FTIR Spectroscopy, Anti-diabetic activity of Acacia catechu ethanolic seed extract. 2015 [cited 2021 Aug 31]; Available from: https://pdfs.semanticscholar.org/983d/dacc94d0aa8287a779084d4b62b975bd7bea.pdf

36. Ganapathy, Dhanraj, Shanmugam, Rajeshkumar, Thangavelu, Lakshmi. Nanobiotechnology in combating CoVid-19. Bioinformation. 2020;828–828.

37. Murali N, Lakshmi T, RajeshKumar S, Roy A, Geetha RV. Characterization of Silver nanoparticles synthesized from Curculigo orchioides extract using UV vis spectroscopy -. Journal of Complementary Medicine Research. 2020;11(5):68–74.

38. Ahamad ST, Tanish Ahamad S, Lakshmi T, Rajeshkumar S, Roy A, Gurunadhan D, et al. Antibacterial Activity of Taxifolin Isolated from Acacia Catechu Leaf Extract-An Invitro Study [Internet]. Vol. 10, Indian Journal of Public Health Research & Development. 2019. p. 3540. Available from: http://dx.doi.org/10.5958/0976-5506.2019.04135.4

39. Ezhilarasan D, Lakshmi T, Subha M, Deepak NV, Raghunandhakumar S. The ambiguous role of sirtuins in head and neck squamous cell carcinoma. Oral Dis [Internet]. 2021 Feb 11 [cited 2021 Aug 31]; Available from: https://pubmed.ncbi.nlm.nih.gov/33570800/

40. Thakur M, Guttikonda VR. Estimation of hemoglobin, serum iron, total iron-binding capacity and serum ferritin levels in oral submucous fibrosis: A clinicopathological study. J Oral Maxillofac Pathol [Internet]. 2017 [cited 2021 Aug 31];21(1). Available from: https://pubmed.ncbi.nlm.nih.gov/28479683/

41. Lakshmi T, Ezhilarasan D, Vijayaragavan R, Bhullar SK, Rajendran R. Acacia catechu ethanolic bark extract induces apoptosis in human oral squamous carcinoma cells. J Adv Pharm Technol Res [Internet]. 2017 [cited 2021 Aug 31];8(4). Available from: https://pubmed.ncbi.nlm.nih.gov/29184846/

42. Role of Nanomedicine in Novel Corona Virus Pandemic: A perspective [Internet]. 2020 [cited 2021 Aug 31]. Available from: http://bbrc.in/bbrc/role-of-nanomedicine-in-novel-corona-virus-pandemic-a-perspective/

43. Anitha R, Prathoshni S, Lakshmi T. The effect of capsicum oleoresin on nitric oxide production and nitric oxide synthase gene expression in macrophage cell line [Internet]. Vol. 10, Pharmacognosy Research. 2018. p. 343. Available from: http://dx.doi.org/10.4103/pr.pr_46_18

44. Mizushima Y, Kobayashi M. Interaction of anti-inflammatory drugs with serum proteins, especially with some biologically active proteins. J Pharm Pharmacol. 1968 Mar;20(3):169–73.

45. Narendra S, Roy A, Shanmugam R, Thangavelu L. Anti-inflammatory activity of nutmeg oleoresin mediated silver nanoparticles- An In- vitro study [Internet]. Vol. 39, Biomedicine. 2020. p. 234–8. Available from: http://dx.doi.org/10.51248/.v39i2.186

46. Saranya S, Vijayarani K, Pavithra S. Green Synthesis of Iron Nanoparticles using Aqueous Extract of Musa ornata Flower Sheath against Pathogenic Bacteria [Internet]. Vol. 79, Indian Journal of Pharmaceutical Sciences. 2017. Available from: http://dx.doi.org/10.4172/pharmaceutical-sciences.1000280

47. Swathy S, Roy A, Rajeshkumar S. Anti-inflammatory activity of Ginger oleoresin mediated Silver nanoparticles [Internet]. Vol. 13, Research Journal of Pharmacy and Technology. 2020. p. 4591. Available from: http://dx.doi.org/10.5958/0974-360x.2020.00808.2

48. Rajendran R, Kunjusankaran RN, Sandhya R, Anilkumar A, Santhosh R, Patil SR. Comparative Evaluation of Remineralizing Potential of a Paste Containing Bioactive Glass and a Topical Cream Containing Casein Phosphopeptide-Amorphous Calcium Phosphate: An in Vitro Study. Pesqui Bras Odontopediatria Clin Integr. 2019 Mar 12;19(0):4668.

49. Ashok BS, Ajith TA, Sivanesan S. Hypoxia-inducible factors as neuroprotective agent in Alzheimer's disease. Clin Exp Pharmacol Physiol [Internet]. 2017 Mar [cited 2021 Sep 15];44(3). Available from: https://pubmed.ncbi.nlm.nih.gov/28004401/

50. Malli SN, Selvarasu K, Jk V, Nandakumar M, Selvam D. Concentrated Growth Factors as an Ingenious Biomaterial in Regeneration of Bony Defects after Periapical Surgery: A Report of Two Cases. Case Rep Dent [Internet]. 2019 Jan 22 [cited 2021 Sep 15];2019. Available from: https://pubmed.ncbi.nlm.nih.gov/30805222/

51. Mohan M, Jagannathan N. Oral field cancerization: an update on current concepts. Oncol Rev [Internet]. 2014 Jun 30 [cited 2021 Sep 15];8(1). Available from: https://pubmed.ncbi.nlm.nih.gov/25992232/

52. Menon S, Ks SD, R S, S R, Vk S. Selenium nanoparticles: A potent chemotherapeutic agent and an elucidation of its mechanism. Colloids Surf B Biointerfaces [Internet]. 2018 Oct 1 [cited 2021 Sep 15];170. Available from: https://pubmed.ncbi.nlm.nih.gov/29936381/

53. Samuel SR, Acharya S, Rao JC. School Interventions-based Prevention of Early-Childhood Caries among 3-5-year-old children from very low socioeconomic status: Two-year randomized trial. J Public Health Dent [Internet]. 2020 Jan [cited 2021 Sep 15];80(1). Available from: https://pubmed.ncbi.nlm.nih.gov/31710096/

54. Praveen K, Narayanan V, Muthusekhar MR, Baig MF. Hypotensive anaesthesia and blood loss in orthognathic surgery: a clinical study. Br J Oral Maxillofac Surg [Internet]. 2001 Apr [cited 2021 Sep 15];39(2). Available from: https://pubmed.ncbi.nlm.nih.gov/11286449/

55. Neelakantan P, Subbarao C, Subbarao CV, De-Deus G, Zehnder M. The impact of root dentine conditioning on sealing ability and push-out bond strength of an epoxy resin root canal sealer. Int Endod J [Internet]. 2011 Jun [cited 2021 Sep 15];44(6). Available from: https://pubmed.ncbi.nlm.nih.gov/21255047/

56. Oligonucleotide therapy: An emerging focus area for drug delivery in chronic inflammatory respiratory diseases. Chem Biol Interact. 2019 Aug 1;308:206–15.

57. Kumar MS, Vamsi G, Sripriya R, Sehgal PK. Expression of matrix metalloproteinases (MMP-8 and -9) in chronic periodontitis patients with and without diabetes mellitus. J Periodontol. 2006 Nov;77(11):1803–8.