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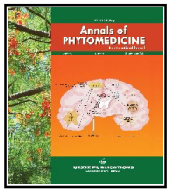

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Characterisation of selenium nanoparticles and *Phyllanthus niruri* Hook. f. selenium nanoparticles with histopathological investigation of their effects on cadmium-induced gastric toxicity in wistar rats

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Abstract

Cadmium, a very hazardous metal, plays an ancillary part in free radicals' formation that harms the stomach tissues. Antioxidants like vitamin E and C, selenium, *etc*., can protect against the harmful effects of cadmium by averting the damage caused by reactive oxygen species (ROS). In this study, a novel technique was proposed for combating cadmium toxicity by combining nanoselenium with *Phyllanthus niruri* Hook. f. extract in rat model. The nanoselenium (SNP) and *P. niruri* fabricated selenium nanoparticle (PNFSNP) were characterised using fourier transform infrared (FTIR) and UV-Vis spectroscopic profiles. Total 48 wistar rats were equally divided into 8 experimental groups. Positive control rats were administered 40 mg/l of cadmium chloride for 28 days in drinking water and treatment groups were administered with 0.1 mg/kg selenium, 0.2 mg/kg nanoselenium and 0.2 mg/kg PNFSNP body weight orally, for 28 days, respectively. On 29th day, the wistar rats were sacrificed, stomach was collected and examined histologically. Oral administration of $CdCl_2$ significantly induced haemorrhagic and necrotic lesions in gastric mucosa, degenerative alterations like epithelium discontinuity, mucin coat depletion, leucocytic infiltration, *etc*. Treatment with the selenium, SNP and PNFSNP significantly healed gastric damages. All treatments had protective effects against cadmium-induced oxidative damage; especially, PNFSNP has a promising therapeutic potential. Therefore, PNFSNP can be a forthcoming natural product for countering the cadmium chloride intoxication due to its potential gastroprotective effect that minimizes gastric toxicity effect of cadmium chloride.

1. Introduction

Natural metallic elements are difficult to completely eradicate from the environment. The toxicities through metal contamination are increasing with increased usage of pesticides (Wahab *et al*., 2022), metals in food, pharmaceutical industry (Briffa *et al*., 2020), residential, and technology applications (Tchounwou *et al*., 2012). Cadmium is a harmful heavy metal with toxicity that impact damage to body tissues of both humans and animals (Mishra *et al*., 2021). Cadmium causes oxidative stress by impairing the antioxidant enzyme system through alterations in gene expressions. Disruption of the cellular oxido-reduction balance can cause serious tissue damage with reduced liver, kidney, testicle, stomach, and brain function (Andjelkovic *et al*., 2019). The detrimental effects of cadmium on the stomach may lead to altered digestive physiology (Jyothilekshmi *et al*., 2020). After causing a benign lesion on the mucosal epithelium, it can induce stomach ulceration with decreased mucin content. Currently, antacid or cytoprotective medicines are used to treat ulcers, with side effects such as joint discomfort, irregular heartbeat, hemopoeitic alterations, gynaecomastia, and impotence.

Selenium is a necessary trace micronutrient with crucial antioxidant property in the form of selenoproteins, which aid in the formation of DNA and guard against cell damage and infection (Tinggi *et al*., 2008). Selenium defends cells against cadmium-induced mutilation by lowering ROS levels and enhancing the activity of antioxidant selenoproteins like glutathione peroxidase. It may reduce cadmium-induced toxicity *via* an antioxidative mechanism (Rahman *et al*., 2019).

Nanoselenium can also be used as a better alternative because of their biocompatibility, bioavailability, and low toxicity, as well as their anticancer, antioxidant, antibacterial, and antibiofilm capabilities (Bisht *et al*., 2022). The plant mediated nanoselenium make nanoselenium safer, more environment friendly, less expensive, and nontoxic being synthesised using plant extracts (Palai and Patra, 2021). Furthermore, because of the natural coating of organic molecules on the surface, which inhibits nanoparticles from

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aggregating over time, naturally formed nanoselenium is more compatible with human organs and tissues and remains functionally active for a longer period (Ikram *et al*., 2021).

Further, many green synthesis of nanoselenium are done with leaf extracts of *Moringa olifera* (Abu-Zeid *et al*., 2021), aqueous fruit extract of *Emblica officinalis* (Gunti *et al*., 2019), fenugreek seed extract (Johnson *et al*., 2022), citrus fruit (Alvi *et al*., 2021), *Aloe vera* leaf extract (Ikram *et al*., 2021), *Clausena dentate* leaf extracts (Johnson *et al*., 2022), *etc*., for various biomedical applications.

The subtropical plant *Phyllanthus niruri* Hook. f. (bhumi amla), which belongs to the Phyllanthaceae family, is used as a folk remedy throughout the world to treat renal ailments, intestinal infections, and chronic hepatitis. It possesses antioxidant (Harish and Shivanandappa, 2006), antimicrobial (Nigam and Garg, 2022), antidiabetic properties (Patel *et al*., 2022). It possesses anti-inflammatory and antiulcer properties and supports ulcer protection through mucosal layer regeneration and significant inhibition of bleeding and edema production (Mostofa *et al*., 2017). The entire plant of *P. niruri* contains flavonoids, tannins, and hydrolyzable phenolics which has an important role in forming phytonanoparticles.

In the available literature, the gastroprotective effect of PNFSNP has not been reported. Therefore, the current experiment was planned for synthesis of PNFSNP utilising whole plant extracts of *P. niruri via* a low-cost, green, simple reduction approach, and its bioefficacy was demonstrated and compared with that of selenium and nanoselenium against cadmium toxicity. To establish its amelioration potential, nanoselenium and PNFSNP were tried on cadmium induced gastric toxicities involving oxidative stress and inflammation.

2. Materials and Methods

2.1 Ethical approval

Use of animals' protocol was approved vide Letter No. 29/IAEC/10.12.19, Sl. No. 3 of IAEC, CVSc & AH, Bhubaneswar, Odisha, India (Regd. No. 433 CPCSEA/CVS/2007).

2.2 Experimental animals

Forty-eight numbers of 6-8 weeks old male albino wistar rats weighing about 180 g were procured from Saha Enterprises, Kolkata (CPCSEA registered organisation). Wistar rats were housed in cages at a constant room temperature (22-24^{0}C, humidity 70-75%). They were kept in an air-conditioned room in a clean polypropylene cage with a stainless-steel grill and a layer of soft bedding and nesting material. The rodents were fed a typical commercial rat meal and given tap water ad libitum.

2.3 Preparation of *P. niruri* ethanolic extract

The whole leaves of *P. niruri* were collected in January, 2020 from local areas of Cuttack, Odisha (Latitude: 20.45675; Longitude: 85.5738) washed properly, dried under shed, and pulverized. The plant was authenticated by Dr. Debasis Dash, Associate Professor, Department of Botany, College of Basic Science and Humanities, OUAT on date 09.01.2020 and deposited at the herbarium, Department of Botany, College of Basic Science and Humanities, OUAT as 563/9.01.2020. The extraction of active compounds was done in Soxhlet apparatus with desired extracting solution (75 ml each of C_2H_5OH, CH_3COCH_3, CH_3COOH and distilled water) for 8 h. The extract was concentrated to 2 to 3 ml in rotary evaporator.

2.4 Preparation of selenium and nanoselenium solution

Selenium solution was synthesized by dissolving 0.5 mg of sodium selenite (Na_2SeO_3) in 10 ml of distilled water for oral administration to the animals. SNP was synthesized by chemical method with slight modification (Dhawan *et al*., 2021). In this method, 3 ml of 25 mM Na_2SeO_3, 100 mM glutathione and 0.15% of bovine serum albumin was added and finally the volume was adjusted with 9 ml of double distilled water. The pH of the synthesized SNP was adjusted to alkaline by adding 1 M sodium hydroxide drop wise.

2.5 Preparation of *P. niruri* fabricated nanoselenium

PNFSNP was synthesized by green synthesis method with slight modification (Gunti *et al*., 2019). *P. niruri* plant extract (4 ml) was added drop wise to 20 ml of 10 mM sodium selenite under magnetic stirring condition and it was further kept in dark at temperature 27 ± 2^{0}C with 120 rpm on orbital shaker for 24 h (Figure 1).

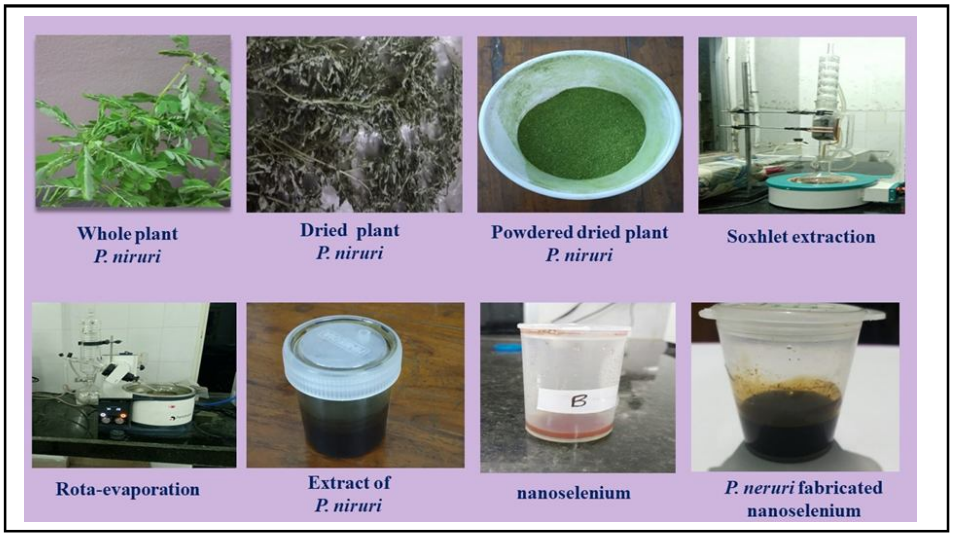


Figure 1: Synthesis of nanoselenium and PNFSNP utilising whole plant extract of *P. niruri*.

2.6 Characterisation of *P. niruri* fabricated nanoselenium

The nanoselenium and PNFSNP were subjected into FTIR analysis (Perkin Elmer, Model: UTAR TWO) with resolution of 4000-450 cm^{-1} to perceive the probable functional groups. Also, they were scanned using UV-Visible spectrophotometer (Make - Perkin Elmer, model-lambda 365) at 1100-190 nm with UV Express-Version 4.1.1 software.

2.7 Experimental design

The 48 number of wistar rats were divided into 8 experimental groups, having 6 rats in each group. The rats in Group-1 were taken as the control group. Positive control rats (Group-2) were given $CdCl_2$ @ 40 mg/l for 28 days in drinking water (El-Boshy *et al*., 2015). The negative control groups, *i.e.*, Group-3, Group-4 and Group-5 were administered with only 0.1 mg/kg bodyweight of selenium, 0.2 mg/kg bodyweight of nanoselenium and 0.2 mg/kg bodyweight of PNFSNP orally, respectively, to ascertain any harmful effect of these agents on stomach. The treatment group rats were given with 0.1 mg/kg bodyweight of selenium (Group-6), 0.2 mg/kg bodyweight of nanoselenium orally (Group-7) and 0.2 mg/kg bodyweight of PNFSNP (Group-8) for 28 days orally, respectively, (El-Boshy *et al*., 2015, Dahdouh *et al*., 2019, Owum and Dim, 2019).

2.8 Histopathological examination

On 29th day, the rats were sacrificed and the abdomen was cut to expose the stomach. The tissue samples of stomach were collected in 10% buffered neutral formalin (BNF) and allowed for fixation for 72 h. Then samples were routinely processed to obtain 5 µm thick paraffin sections which were subsequently stained with Haematoxylin and Eosin stain to observe the general histo-architecture and PAS-AB stain (Bancroft and Stevens, 1996) to note the distribution of neutral as well as sulphated mucopolysaccharides in the gastric mucosa.

3. Results

3.1 Synthesis of nanoselenium and *P. niruri* fabricated nanoselenium

The synthesis of nanoselenium and the fabrication of nanoselenium by *P. niruri* were preliminary confirmed by colour change and characterisation was done using Fourier transform infrared and UV-Vis spectroscopy. Formation of selenium nanoparticles was assured by the colour change of the reactant solution from clear white to brick red and its liquid consistency. Formation of phytofabricated nanoselenium was ensured by the colour change of the reactant solution from colourless to dark green colour and its thick liquid consistency (Figure 1).

3.2 Characterisation of nanoselenium and *P. niruri* fabricated nanoselenium

The FTIR analysis of nanoselenium resulted two peaks at 3326.64 cm^{-1} and 1634.97 cm^{-1} in infrared spectrum indicating the presence of hydroxyl (-OH) and alkene (-C=C) functional group on the surface of nanoselenium, respectively (Figure 2). FT-IR analysis of *P. niruri* extract fabricated nanoselenium also showed peaks at 3327.06 cm^{-1} and 1637.76 cm^{-1} indicating the presence of functional group such as hydroxyl (-OH) and alkene (-C=C), respectively, on the surface of PNFSNP (Figure 3). Under UV-Visible spectroscopy, nanoselenium and PNFSNP showed characteristic spectral bands confirmed by absorption spectra showing absorbance peak λ_{max} at 234.25 nm and 239.20 nm that confirms the synthesis of nanoselenium and PNFSNP, respectively (Figures 4, 5).

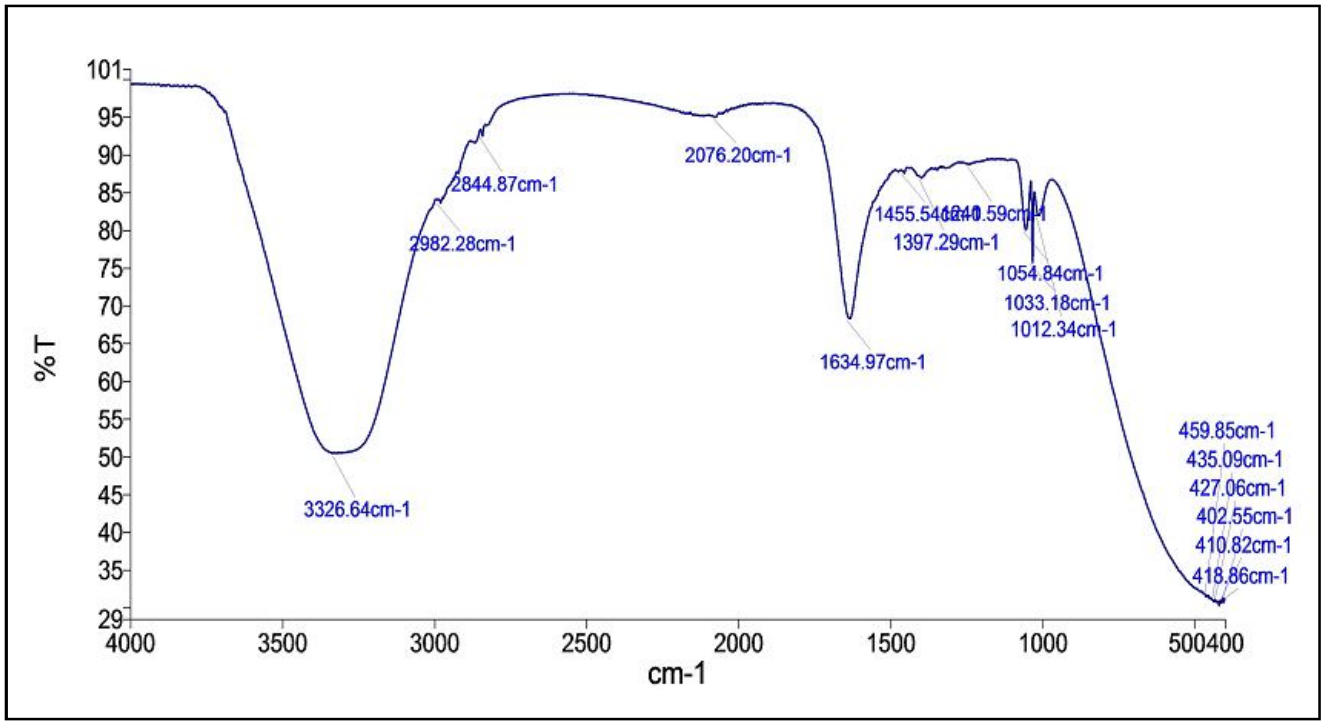


Figure 2: Characterisation of nanoselenium through FTIR spectroscopy.

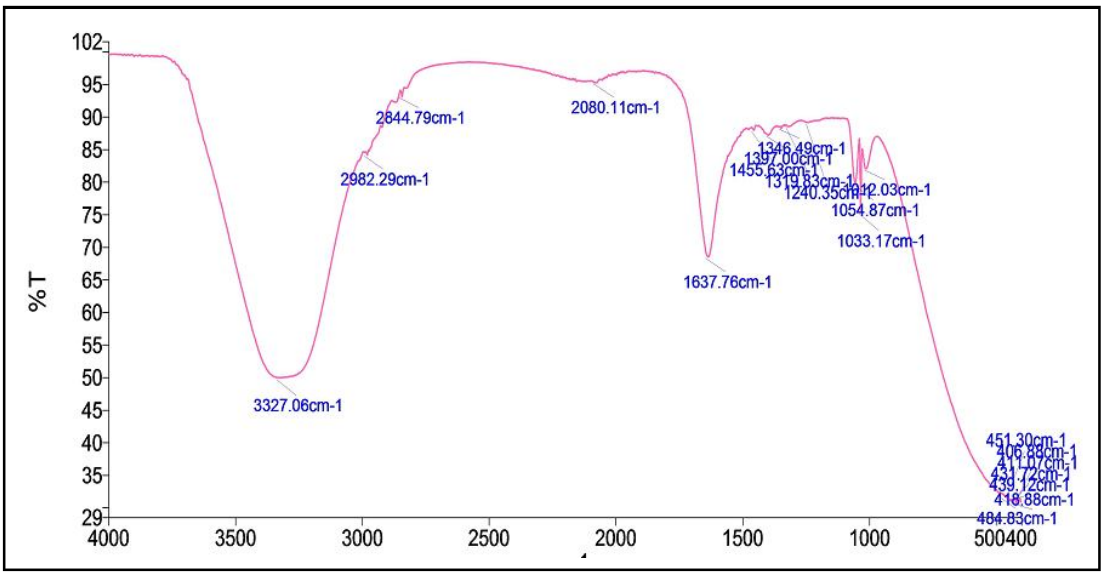


Figure 3: Characterisation PNFNP through FTIR spectroscopy.

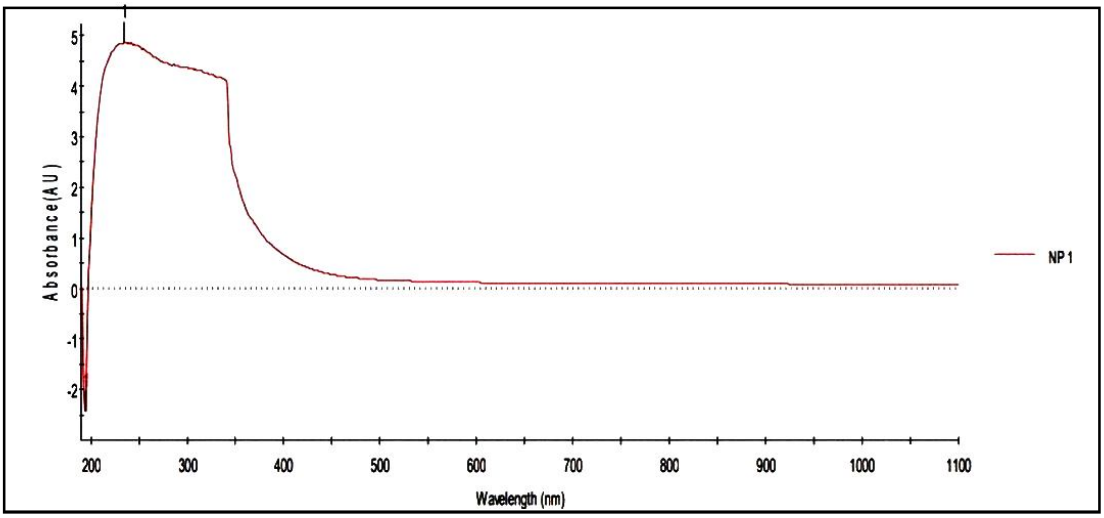


Figure 4: Characterisation of nanoselenium through UV-Vis spectroscopy.

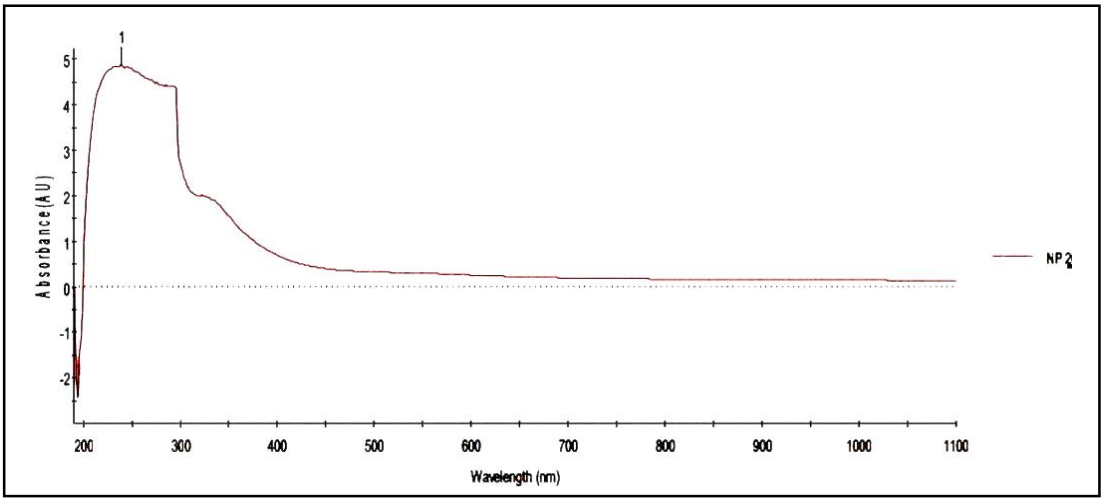


Figure 5: Characterisation of PNFNP through UV-Vis spectroscopy.

3.3 Histopathological examination

In the microscopic study, control group showed normal histological layout, intact gastric epithelial lining, and gastric glands (Figure 6a). The stomach in cadmium chloride treated rats showed pathological alterations including desquamation of the epithelial lining, necrotic changes in the mucosa, infiltration of leucocytes in the mucosa and submucosa, degeneration of gastric glands, reduction in the frequency distribution of glandular cells like parietal cells and chief cells (Figures 6b, 6c, 6d) and depletion of the surface mucin content (Figure 6e).

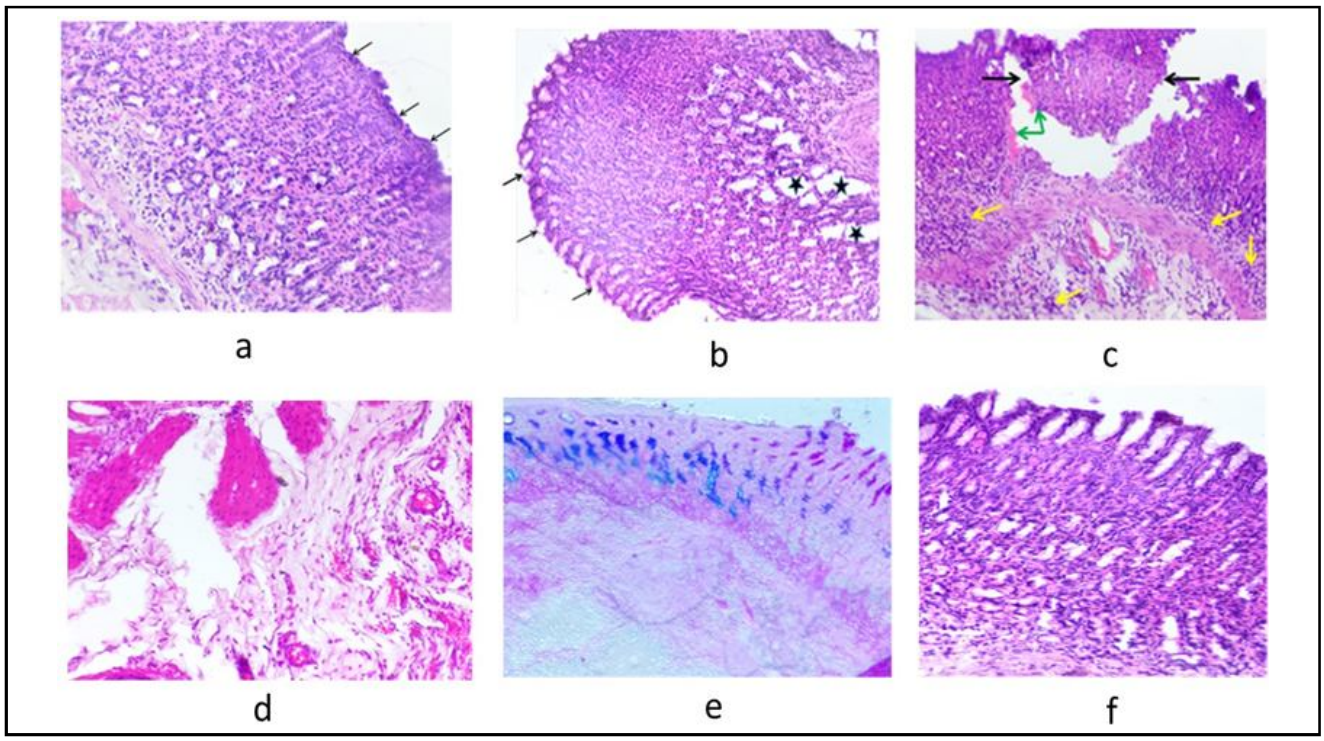
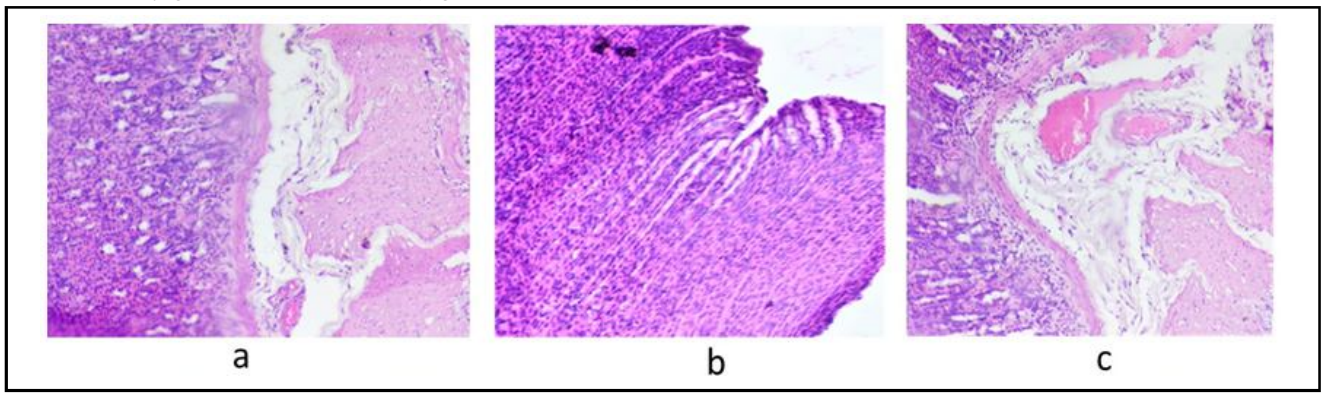


Figure 6: Microphotograph of stomach of rat showing a. normal histoarchitecture with an intact surface epithelium (arrow) in Group-1, H & E × 100, b. discontinuity in the surface epithelium (arrow), degenerative changes in the gastric glands (star mark) in Group-2, H & E × 100, c. mucosal desquamation (black arrow), haemorrhages (green arrow) in the gastric mucosa and heavy infiltration of leucocytes (yellow arrow) in Group-2, H & E × 100, d. frquent haemorrhages in the submucosa (arrow) in Group-2, e. depleted mucin coat on the surface epithelium in Group-2, PAS-AB × 100, f. Normal configuration of mucosa in Group-3, H & E × 100.

The in filtered leucocytes were mainly observed in clusters at the basal part of the lamina propria. Majority of the gastric glands revealed presence of acidic mucopolysaccharides and few glands were noted with sparse amount of neutral, PAS positive mucopoly-saccharides (Figure 6e).

The gastric tissue of the rats receiving selenium, nanoselenium and phytonanoselenium without any cadmium chloride administration revealed healthy gastric histoarchitecture (Figures 6f, 7a, 7b, 7c) with a prominent protective coating of glycoproteins on the surface of the mucosa (Figure 7d). It indicated no harmful effect of these compounds on the gastric components. The selenium treated rats exhibited some gastric alterations in a less severe form. Haemorrhagic and necrotic lesions were observed occasionally. Infiltration of neutrophils was found in less numbers. The epithelial desquamation and depletion of surface glycoprotein layer was observed but to a lesser extent (Figures 7e, 7f, 8a).



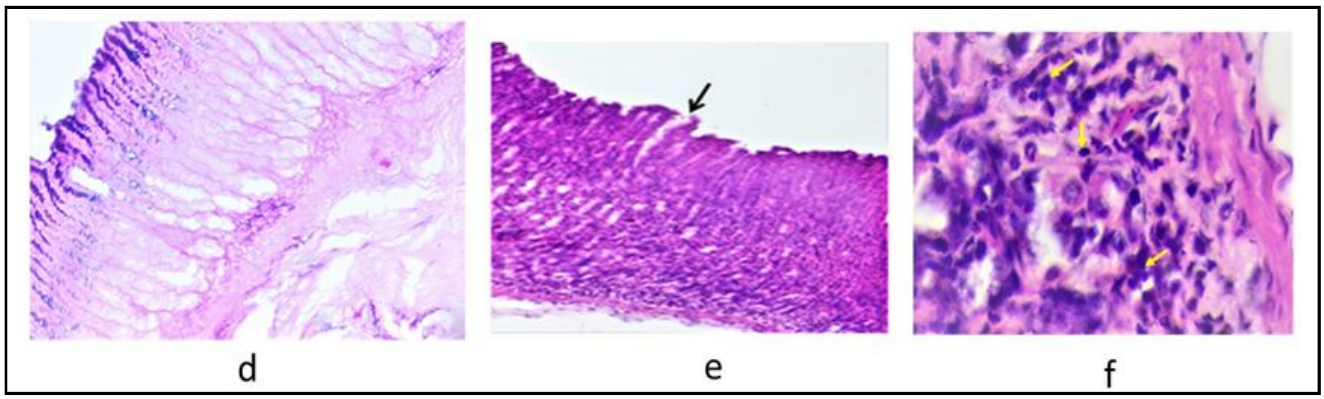


Figure 7: Microphotograph of stomach of rat showing a. healthy submucoa without any haemorrhages and inflammatory changes in Group-3, H & E × 100, b. intact epithelium and normal glandular arrangement in Group-4, H & E × 100, c. normal glandular and sumucosal morphology in Group-5, H & E × 100, d. normal distribution of mucin content in the mucosa of Group-5, PAS-AB × 100, e. epithelial discontinuity at few location (arrow) in Group-6, H & E × 100, f. sparse infiltration of inflammatory cells in the base of the mucosa (arrow) in Group-6, H & E × 1000.

The nanoselenium treated rats showed that the cadmium induced gastric damage was neutralised to a great extent. It was indicated by intact epithelial lining, presence of full thickness mucin coating over the epithelium, no haemorrhages, and sparse mononuclear cells infiltration (Figures 8b, 8c). The overall histomorphology of stomach in PFSNPs treated rats was represented in complete normal form as that of the control group. The gastric mucosa had regained its full thickness and morphology, with normal glycoprotein content, normal gastric gland morphology and disposition, with no haemorrhages or necrotic changes (Figures 8d, 8e, 8f). Infiltration of leucocytes in the mucosa and submucosa were sparse.

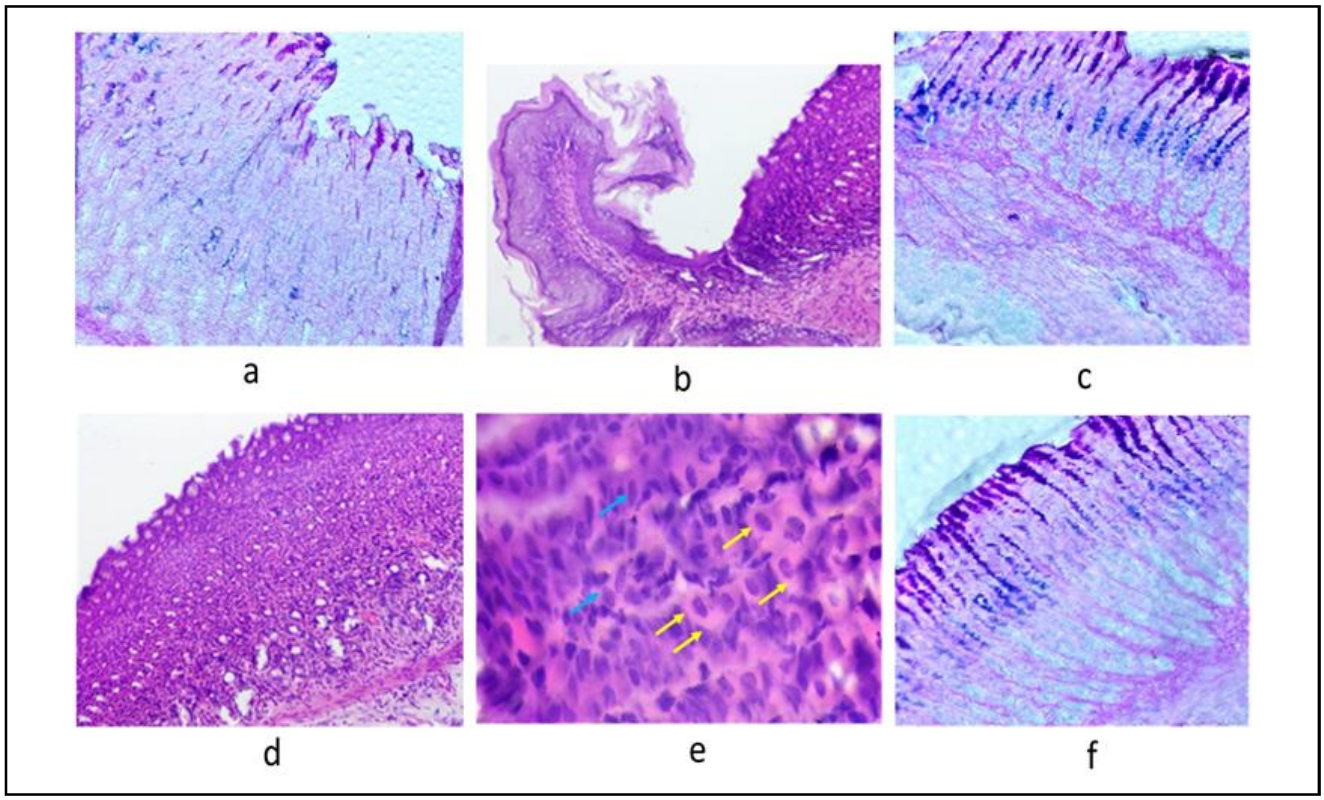


Figure 8: Microphotograph of stomach of rat showing a. moderate quantity of mucin on the surface epithelium of Group-6, PAS-AB × 100, b. near normal histomorphology of gastric wall in Group-7. H & E × 100, c. abundant amount of glycoproteins in the gastric mucosa of Group-7 PAS-AB × 100, d. full thickness of gastric mucosa with continuous epithelial lining and normal disposition of gastric glands in Group-8. H & E × 100, e. normal frequency distribution of gastric gland cells, parietal cells (yellow arrow) and chief cells (blue arrow) in group-8. H & E × 1000, f. proper distribution of neutral and acidic mucopolysaccharides. Note the content of mucin on the epithelial surface in Group-8. PAS-AB × 100.

4. Discussion

Cadmium toxicity has emerged globally as a result of increased use of pigment in paint manufacture, electroplating, polyvinyl chloride plastics and nickel-cadmium batteries (Mishra *et al*., 2021). Cadmium, which is found in many foods and cigarette products, can induce gastric toxicities like ulcers when consumed (Engwa *et al.,* 2019). Selenium protects cells from cadmium-induced oxidative stress by reducing ROS levels and increasing the activity of antioxidant selenoproteins such as glutathione peroxidase (Rahman *et al*., 2019). Owing to its better biocompatibility, bioavailability, and low toxicity, nanoselenium may be a preferable choice showing more antioxidant and antibacterial properties (Bisht *et al*., 2022). *P. niruri* possessing antioxidant and antiulcer properties can aid in ulcer protection through mucosal layer regeneration and significant inhibition of bleeding (Mostofa *et al*., 2017). The entire plant of *P. niruri* contains a high concentration of hydrolyzable phenolics, flavonoids, and tannins, *etc*., which when incorporated into nanoselenium particles can augment its efficacy too.

The purpose of this study was to determine the efficacy of selenium, nanoselenium, and PNFSNP in reducing cadmium toxicity in wistar rats. The formation of nanoselenium and PNFSNP was assured by the colour change of the reactant solution. The presence of hydroxyl and phenolic groups in phytochemicals of *P. niruri*, as demonstrated by FTIR and UV-Vis analysis, may bind to nanoselenium and enhance its biofunction as phytofabricated nanoselenium (Ananth *et al*., 2019). The phytochemicals play a crucial function in enhancing the efficacy of phytonanoparticle (Rudrapal *et al*., 2022).

Our experimental model, male wistar rats were administered cadmium orally for 28 days. Consequently, cadmium induced gastric toxicity was expressed histologically in the forms of epithelial desquamation, glandular degeneration, mucin layer depletion, reduction in the frequency distribution of parietal cells and chief cells. Similar observations like abnormalities in the gastric fundus, mucuos membrane discontinuity, necrosis of gastric mucosa epithelial cells and surface epithelium degradation in wistar rat stomach were also recorded by Asar *et al*. (2000) and Tarasub *et al*. (2009) after exposure to cadmium chloride. Cadmium poisoning also caused detrimental alterations in the structure of the stomach tissue in mice (Mohapatra *et al*., 2009).

Cadmium is absorbed through the gastrointestinal system and reacts with HCl and forms cadmium chloride, causing GIT inflammation (Rahimzadeh *et al*., 2017). It attaches to the mitochondria and, at low concentration, can impede both cellular respiration and oxidative phosphorylation, resulting in gastrointestinal toxicities (Patrick, 2003). Cadmium-induced lipid peroxidation may impact the cytoplasmic and mitochondrial membranes, producing tissue damage and releasing lipid hydroperoxides into the circulation, reflecting the production of oxidative stress (Branca *et al*., 2020).

As cadmium induces oxidative stress, selenium can be interestingly considered for amelioration as it partially antagonizes the toxic effects of cadmium being effective part of many antioxidant therapies (Bernhoft, 2013). Selenium is an antioxidant that mitigated cadmium-induced stomach damage by protecting against cadmium-induced lipid peroxidation. In wistar rats with cadmium chloride poisoning, selenium improved antioxidant state and prevented lipid peroxidation (Bolkent *et al*., 2008). In the current study, it was evident histologically. As in the group of rats treated with selenium, their gastric tissue revealed decrease in the extent of epithelial disintegration. The gastric glands in the lamina propria were comparatively more organized than the cadmium chloride induced group. The frequency of haemorrhages was comparatively less. The mucin coat over the epithelial surface was thicker. These findings suggest that selenium's antioxidant activity may be limiting free radical generation and may be contributing towards its ameliorating capability against cadmium induced gastric toxicity. It is beneficial in reducing lipid peroxidation in a variety of biological systems (Abu-El-Zahab *et al*., 2019).

Due to its superb biodistribution, high sensitivity, and low pharmacological toxicity, nanoselenium is considered as a promising novel therapeutic candidate against metal toxicity. Because of their small size and quantum size effect, nanoselenium has a distinct character that could lead to superior biological activities (Hosnedlova *et al*., 2018). Nanoselenium can be tried to treat cadmium poisoning as cadmium is removed from waste water by nanosized TiO_2 particles and Al_2O_3 nanoparticles (Yang *et al*., 2019). In this study, SeNPs revealed the gastroprotective effects through reduction in intensity and frequency of haemorrhage, improvement in continuity of gastric epithelial lining, retrieval of gastric gland morphology, decreased concentration of leucocytes infiltration in lamina propria and submucosa and partial restoration of mucin coat thickness. These findings corroborate with the observations recorded by Bai *et al*. (2020) in ethanol-induced gastric mucosal injury in rats. It might be due to active functional groups on the surface of nanoselenium that reduces cadmium chloride toxicities through its antioxidant protective mechanism, ROS reduction and scavenging the free radicals (Yetisgin *et al*., 2020). It also inhibits lipid peroxidation, and attenuate inflammatory nitric oxide generation exhibiting protective effects in rats (Khalil *et al*., 2022).

Further, nanoselenium particle is very popular due to its high potential for nutritional supplement and gastroprotection, non-toxic and environment friendly (Hano and Abbasi, 2021). The leaves, stem, and roots of *P. niruri* contain a variety of phytochemical components such as flavonoids, lignans, coumarins, terpenes, tannins, alkaloids, saponins, and phenylpropanoids extending pharmacological properties (Bagalkotkar *et al*., 2006). These phytocompounds may be responsible for the bioreduction of Se^{4+} ions while capping with nanoselenium. In this study, the Se^{4+} ions were bioreduced using *P. niruri* whole plant extracts as a bio-reducing agent to effectively create nanoselenium as other metallic nanoparticles like silver, gold, zinc, and so on. These are used as nanocarrier for delivering and targeting drugs (Chandrakala *et al*., 2022) and phytochemicals (Srinivasan and Murali, 2023) to their site of action for effective amelioration against gastric damage.

The rats pretreated with PNFSNP confirmed significant improvement in the histo-architecture of gastric tissue than selenium and nanoselenium. In this treatment group, the stomach tissue of rats discerned an intact lining of gastric epithelium covered with a strongly thick mucin coat. Gastric glands also showed normal secretory cells, no haemorrhages and minimal inflammation. These findings suggest that PNFSNP could minimise the oxidative stress in cadmium-treated gastric toxicities by reducing free radical build up. The antioxidant protection system reduces ROS and scavenges the free radicals that cause gastrointestinal damage, hence inhibiting lipid peroxidation (Yoshikawa *et al*., 1993; Beiranv and Bahramikia, 2020).

5. Conclusion

This study concluded that cadmium-induced degenerative alterations were reduced in the selenium, nanoselenium, and *P. niruri* fabricated nanoselenium administered rats which act as antioxidants and successfully restore the normal architecture of stomach. Both selenium and nanoselenium may serve as scavenger for oxygen-derived free radicals, inhibiting free radical generation and thereby protecting the stomach from injury. PNFSNPs are more powerful antioxidants and free radical scavengers than the other two and reduce cadmium toxicity in rats' stomach more effectively than selenium and nanoselenium. Therefore, continued research into the prospective protective benefits of PNFSNP against cadmium chloride-induced gastric damage may contribute in the development of therapeutically practicable ways to treat patients with cadmium chloride-induced gastric toxicities.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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