**Materials and Methods**

Synthesis of ruthenium-phloretin complex

Approximately, 5.08 g (0.02mol) of phloretin was applied drop wise, with mixing, to a solution of ruthenium chloride so that a molar ratio of 1:2 (metal: ligand) was achieved. The resulting solution was filtered and stored over silica gel. The obtained product was dark brown in color and Supplementary figure 1A represents the possible structure of the ruthenium-phloretin complex.

Characterizations of ruthenium-phloretin complex

The UV-Visible spectrum was recorded via UV-1800 Shimadzu double beam spectrophotometer. FT-IR spectroscopy (ALPHA-T, Bruker, and Rheinstetten, Germany) wax used to document the infrared spectrum of the complex. The molecular structure of the ruthenium-phloretin complex was studied by employing tandem mass spectrometry (ESI-MS) techniques with electrospray ionization. A Bruker- Avance-600 MHz spectrometer was used for the studying of the 1H-NMR spectrum of the complex. Scanning electron microscopy (JEOL MAKE, (UK) MODEL- JSM6360) was used to examine the morphological appearance of the sample at an accelerating voltage of 17 kV. X-Ray diffraction of the complex was performed in X'Pert Pro XRD (PANanlytic) machine.

Toxicological investigation

Acute oral toxicity study (LD50)

Thirty Sprague Dawley rats of both sexes were distributed into five groups (six animals per group, three of each sex) including control and study group (treated with 2000, 600, 400, 200 mg / kg ruthenium phloretin complex) and placed under monitoring for three days.

Sub-acute toxicity studies

Sprague Dawley rats were paired to five experimental groups: complex treated (25, 50, 100, 300 mg / kg) and vehicle control group. The animals were orally administered with ruthenium-phloretin complex and sacrificed at 28th day by ether anaesthesia.

Analysis of haematology and serum biochemistry

Blood samples were collected from rats for the assessment of haematological parameters. Serum Biochemistry parameters were analysed using a Microlab 3000 auto analyser.

Histopathological study of rat organs

Primary organs such as liver, kidney, stomach and testis were harvested from each participant after 28 days and sectioned into 5-micron thickness on glass slide and subsequently stained with haematoxylin and eosin (H&E) for microscopic examination.

**Results**

Instrumental analysis

The ruthenium phloretin complex and free phloretin FTIR spectra are shown in the (Supplementary Figure 1C) and assessed in Supplementary Table 1. The v (C=C) stretching occurred at 1571.75 cm-1 for the complex. The v (C=O) stretching occurred at 1384.23 cm-1 and 1248 cm-1 for phloretin where as for the complex it seen at 1377.28 cm-1 and 1240.53 cm-1 correspondingly. The v (C-OH) bond shifted from 980.13 cm-1 to 972.67 cm-1 for the ruthenium phloretin complex. The characteristic band for the complex was seen at 614.22 cm-1 which was absent in free phloretin. Both phloretin and complex showed strong absorption bands at 280-430 nm in UV-visible spectroscopy (Supplementary Figure 1D). The ruthenium-phloretin complex exhibited only charge transfer transitions, from the ligand (RIF) to the metal. Therefore, no d-d transitions are expected for Ru(III) complexes. Supplementary Table 2 shows the chemical transition of 1H NMR spectrum of the complex and the unbound ligand. The observations reveal the omission of 3-OH, 9-OH protons in the spectra of the complex, signifying that ruthenium confiscates two protons from the flavonoid phloretin upon complexation, while the other protons were found to be slightly shifted and are intra molecularly bonded (Supplementary Figure 1E) suggesting that the chelation occurred via the 3-OH and 9-OH functional groups of the ligand. The mass spectroscopy of the ruthenium phloretin complex is shown in Supplementary figure 1F, the base signal at m/z 275 was of free phloretin whereas m/z 302 was of phloretin+ two water molecules. The signal at 487 m/z seen for one phloretin+ ruthenium each. The molecular peak for ruthenium phloretin complex was seen at 794 m/z where two phloretin+ one ruthenium + two water molecules coordinated to form the complex. Supplementary Figure 1 (G, H & I) exhibits the surface structural arrangement of ruthenium-phloretin complex, evaluated by SEM which denotes crystalline in nature and asymmetrical shape of the complex. The X-ray diffraction study of the complex indicates multiple distinctive sharp peaks which occurred at different diffraction angles attributable to its recognizable crystalline structure (Supplementary Figure 1J).

Toxicity study

Acute and sub-acute toxicity study

The LD50 dose was found to be 400 mg / kg of ruthenium-phloretin complex. During sub-acute toxicity analysis (28 days), no treatment-related fatalities were reported in animals treated with the complex.

Haematological and serum biochemical analysis

Supplementary Tables 3, 4, 5 & 6 show the haematological and serum biochemical profile of the treated and control groups. WBC, RBC amounts were significantly augmented in complex (300 mg/kg) treated groups contrasted against control animals. ALT, AST, ALP, Glucose and BUN was significantly higher than the control group at 300 mg / kg (p<0.05). Therefore, 300 mg / kg dose of the complex caused toxicity to some degree and was therefore not regarded as a dose for ensuing study.

Histopathology

Histopathology of kidney (Supplementary Figure 2[i] A) of the control group exhibited the normal structural architectural organization. The foremost morphological variations were observed at the 300mg/kg dose (Supplementary Figure 2 [i] E). 25 and 50 mg/kg doses did not denote any major abnormalities in the animals (Supplementary Figure 2 [i] B&C), whereas minor thickening of bowman’s capsule was detected in the mice treated with doses of 100 mg/kg complex (Supplementary Figure 2 [i] D). The histopathology of liver (Supplementary Figure 2 [ii] A), denoted standard hepatic structures in the control group whereas maximum doses (300 mg/kg) of complex denoted focal inflammation (fi), degeneration of hepatocytes (d) and periportal mononuclear infiltrates (pmi) (Supplementary Figure 2 [ii] E). 25, 50 and 100 mg/kg dose administered animals did not exhibit any vital deformity (Supplementary Figure 2 [ii] B,C&D). Supplementary Figure 2 [iii] A reveals the microscopic assessment of stomach, where 300 mg/kg dose of complex showed the congestion (c), haemorrhages (h) and hyperplasia of the gastric glandular zone (hyp) (Supplementary Figure 2 [iii] E). But at the lower dose level (25 mg/kg, 50 mg/kg and 100 mg/kg) histopathological variations were not observed (Supplementary Figure 2 [iii] B, C & D). Supplementary Figure 2 [iv] A reveals the microscopic assessment of testis, where 300 mg/kg (Supplementary Figure 2 [iv] E) of complex treated animals exhibited degeneration in seminiferous tubules (D), and oedema in interstitial tissues (E) and at 100 mg/kg (Supplementary Figure 2 [iv] D) degeneration (D) and hyperplasia (hyp) were noted, but at the lower dose level (25 mg/kg and 50 mg/kg) no histopathological alterations were observed (Supplementary Figure 2 [iv] B&C).