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Analysis of the protective effects of extracts from the therapeutic plant *Aegle marmelos* against cisplatin-induced toxicity

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Abstract

An important field of research in the fight against chemotherapy's negative side effects is the assessment of medicinal plant extracts for their protective benefits against cisplatin-induced toxicity. Many different types of cancer are treated with cisplatin, a chemotherapeutic drug based on platinum. The significant adverse effects of cisplatin, including nephrotoxicity, hepatotoxicity, and ototoxicity, frequently restrict its clinical utility, despite its efficiency. Damage to non-target tissues, including oxidative stress, inflammation, and apoptosis, causes these harmful effects. So, finding preventive medicines that can reduce these side effects of cisplatin without reducing its anticancer effectiveness is an urgent requirement. There is a wealth of bioactive substances found in medicinal plants that may have medicinal uses; these plants have a long history of use in traditional medical systems around the world. The established antioxidant, anti-inflammatory, and cytoprotective activities of these plants form the basis for their research as protective agents against cisplatin toxicity. The primary goals of this research are to determine which medicinal plant extracts are most effective at reducing cisplatin-induced toxicity and, secondarily, to determine the mechanisms of action and possible therapeutic uses of these extracts.

Keywords*:* Medicinal plant extracts, protective effects, cisplatin-induced toxicity, antioxidant activity, *Aegle marmelos*

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Introduction

Cisplatin, also known as cis-diamminedichloroplatinum (II), is a frequent cancer treatment [Pabla & Dong, 2008]. Malignant mesothelioma, tiny lung cells, ovary, testes, cervix, bladder, head, and neck malignancies are included. This drug cures 90% of testicular cancer patients. Michel Peyrone developed cisplatin in 1845. Alfred Werner, who won the Nobel Prize for this work, refined it in 1913. In the 1960s, physicist and biologist Barnett Rosenberg studied how Escherichia coli splits in response to a platinum electrode's electric field [Rosenberg *et al.*, 1965; 1967; 1969]. He accidentally discovered an anticancer chemical. Platinum has a square planner structure in the metallic complex cisplatin/cis-[$PtCl_2$ $(NH_3)_2$]. Possible forms are cis and trans. When left at room temperature, the crystalline material turns white to yellow-orange. Dimethyl primanide, N-dimethyl formamide, and dimethyl formamide dissolve the substance, but water does not. It remains stable under normal pressure and temperature, but may transition to Trans form. Isplatin weighs 301.1 gm/mol and has a density of 3.74 g/cm3, according to Dasari *et al.*, (2014). At 25˚C, the substance is soluble in water and melts at 270>C, with a concentration of 2.53g/L. Cisplatin showed promise in preliminary clinical studies in 1972, but its lethal side effects—vertigo, bone marrow destruction, and renal toxicity—delayed its widespread use. Since its 1978 FDA clinical certification, the drug has been a successful anticancer treatment for various solid malignancies. Modernizations in combination therapy-based protocol and administration methods earned this recognition. Cisplatin is used after radiation or surgery as adjuvant, first-line, or non-adjuvant therapy. Cisplatin can be used alone or with additional drugs. Examples are Duedijk and Lohman's 1985 and Dasari *et al.*, 2014 articles. Scientists have shown that *Aegle marmelos* (Bael) can suppress cancer cell proliferation. Leaf extracts of the plant described earlier are evaluated for phytochemicals and antioxidant properties. In vivo experiments examined whether the leaf extracts prevented cisplatin-induced nephrotoxicity. To find active compounds, leaf extracts have to be fractionated *et al.*, (2011) tested an ethanolic extract from the whole stem of *Bauhinia variegata* (Linn.) on rats with cisplatin-induced nephropathy for nephroprotective effects. The 7 mg/kg cisplatin dosage caused acute nephrotoxicity. After 14 days of dose-dependent ethanol extract at 400 and 200 mg/kg (b.w.), rats had reduced histological and biochemical markers of cisplatin nephrotoxicity. Administration of 400 mg/kg ethanol extract resulted in negative effects on body weight (7.16 ± 1.10; P0.001) and urine volume output (11.95 ± 0.79; P0.05) compared to the toxic control group. The B. Ethanol extract was 400 mg/kg hazardous. Variegata was equally nephroprotective as cystone. Whole B stem injection prevented cisplatin-induced nephropathy. One-way analysis of variance with Tukey-Kramer multiple comparison. Mostafa I. Waly *et al.*, (2013) found that rhubarb's antioxidant and anticancer anthraquinone emodin reduces drug-induced cellular oxidative stress. Cisplatin promotes nephrotoxicity and oxidative stress in 293 petri dish-grown human kidney cells. In vitro, emodin was tested for its antioxidant effects on HEK 293 cells exposed to cisplatin-induced oxidative damage. As established in our research, emodin protected the kidneys from cisplatin-induced oxidative stress by scavenging free radicals. Using 0.5 µm

dosages of Emodin, antioxidant capability and glutathione depletion produced by cisplatin were restored without impacting cell survival. Emodin inhibited S-transferase, reductase, glutathione peroxidase, and superoxide dismutase better than cisplatin. This study suggests that adding emodin to cisplatin may benefit chemotherapy patients. Cisplatin (CDDP), a potent anticancer medication, causes apoptosis, oxidative stress, and kidney nephrotoxicity (Jie Song *et al.*, 2014). Standardized Ginkgo biloba leaf extract EGb761 (EGb) promises wellness as a supplement. This study investigated whether and how EGb inhibits CDDP's nephrotoxicity. Following CDDP injection, EGb restored renal creatinine, BUN, MDA, NO, SOD, CAT, GPx, and GSSG/GSH ratio. In kidneys treated with CDDP, EGb decreased caspase-3 protein levels and NF-κB translocation. In vitro investigations utilizing LLC-PK1 cells, pig kidney proximal tubular epithelial cells, demonstrated that EGb decreased CDDP-induced ROS and iNOS. In LLC-PK1 cells, EGb inhibited CDDP-induced phosphorylation of p65 NF-κB and IκB degradation. However, EGb did not impact CDDP-induced caspase cascade. Its antioxidant and anti-inflammatory properties may explain EGb's renoprotective effects. Cisplatin's main drawback as an anticancer treatment is nephrotoxicity, according to Shabnam Hajian et al. (2014). Cisplatin depletes sodium, potassium, and magnesium and damages tubuli. Eight cisplatin renoprotective therapies exist. 1. Cisplatin metabolism prevention. 2. Reduced renal cell absorption. 3. Cell death pathway obstruction. 4. Cyclin-dependent kinase blockers. 5. Pharmacologic, molecular, and genetic p53 blockers. 6. MAPK inhibitors. 7. Antioxidants for kidney protection from oxidative stress and cisplatin. 8. Reduce inflammation. Many diseases are caused by oxidation-induced free radical chain reactions. More doctors are investigating natural antioxidants for patients. Natural antioxidants reduce kidney ROS while cisplatin fights cancer. Therefore, antioxidants may help. I. Senior Okafor. Portulaca oleracea was tested for renoprotection in cisplatin-nephrotoxic Wistar rats (*et al.*, 2014). Twenty-four female Wistar rats were randomly assigned to six groups. Control group A received no therapy. Cisplatin was given once to control group B at 2ml/kg. Groups C and D received 400 mg/kg and 800 mg/kg MEPO orally six hours after a 2 ml/kg cisplatin injection. Group E received 400 mg/kg MEPO orally for seven days, while Group F received 800 mg/kg six hours before receiving 2 ml/kg cisplatin. To evaluate the treatment, rats' histoarchitecture, creatinine, uric acid, and kidney weight were examined. Rats given 400 mg/kg body weight had their serum creatinine assessed. Compared to cisplatin-treated rats, 800 mg/kg MEPO was significantly lower (p0.05). C, D, E, and F exhibited considerably lower serum uric acid levels than control group A. All groups except the 800 mg/kg b.wt. group increased kidney weight significantly. Take MEPO six hours before cisplatin. Kidney histology slides demonstrated that each dosage avoided or recovered from induced toxicity. Portulaca oleracea extract may be a potential combination therapy for cisplatin-induced kidney impairment because it can treat or prevent it without side effects. Yeon Park *et al.*, (2015) examined eupatilin and *Artemisia asiatica* extract's renoprotective properties on LLC-PK1 kidney epithelial cells. Due to nephrotoxicity, cisplatin is ineffective against many malignancies. Artemisia flavonoids are antioxidants and anticancer. The LLC-PK1 cellular model proves A. Like cisplatin, eupatilin and asiatica extract inhibited oxidative stress-induced cell viability loss dose-dependently. After cisplatin treatment, polyphosphorylated JNK and p38 proteins dropped significantly in A-cotreated cells. Ayurveda/eupatilin. When LLC-PK1 cells receive eupatilin or A. Asiatica extract significantly reduced cleaved caspase-3 expression and cell death after cisplatin treatment. *A. Asiatica* extract and eupatilin may prevent nephrotoxicity by reducing cisplatin-induced kidney damage and side effects. Cisplatin (CSP) treats several malignancies, according to Shreesh Ojha et al. (2016). When CSP damages the kidneys or otitis, treatment is less successful. Despite understanding how CSP damages kidneys, renoprotective treatments are unknown. Since renoprotective therapies only partially reduce CSP-induced renal damage, synergistic or combinatorial drugs are needed. The optimal renoprotective adjuvant should not alter CSP's anticancer effects. Recent preclinical findings on phytochemicals for CSP-induced nephrotoxicity are discussed here. Possible renoprotective drug models include phytochemicals for chemotherapy-induced renal failure. Clinical usage of cisplatin is limited by nephrotoxicity, according to Sara Hosseinian et al. (2016). This research focused on Nigella sativa's (N. sativa) capacity to protect kidneys against cisplatin-induced nephrotoxicity. Vitamin E (100 mg/kg BW) and aqueous-ethanolic N. Sativa extract was tested on renal function and blood and urine biochemistry in rats given cisplatin at 100 and 200 mg/kg, body weight. Six days into the study, cisplatin was injected intravenously at 6 mg/kg body weight. The control and cisplatin groups had significantly different urine glucose, urea, creatinine, and discharge levels. Serum urea and creatinine were considerably lower in the preventative, vitamin E, and N groups. group treated with cisplatin and sativa (200 mg/kg BW). Therapeutic and preventive N. Sativa (100 mg/kg, BW) reduced serum creatinine highest. The preventative and preventive+treatment N groups performed worse than cisplatin. Sativa (200 mg/kg, BW) groups had significantly decreased urine glucose and discharge. Prevention, prevention with treatment, and preventive N increased osmolarity excretion substantially. versus the placebo group. Sonam Sharma et al. (2017) say Acrid Exacum lawii (Gentianaceae) from western and southern India treats kidney and ocular issues. Backing up the common wisdom on E. Legend says the entire E. To protect rats from cisplatin-induced kidney impairment, lawii plant subacute toxicity should be investigated using high-performance liquid chromatography. The lawii plant was standardized with secoiridoid glycoside swertiamarin to OECD guidelines. The extract was tested for nephroprotection in rats given cisplatin (6 mg/kg, intraperitoneal). We examined proinflammatory cytokine variations, renal tissue oxidative stress, and serum renal toxicity markers. In treated rats, DNA and single living cells from their kidneys were removed to evaluate renal tissue oxidation. DNA fragmentation and ROS flow cytometry were also tested. Kidney tissue histology was also examined. The extract included 119.59 mg/g swertiamerin. Appendix E. Lawii plant extracts (ELE) boosted biochemical markers. In addition, it reduces proinflammatory cytokines and protects rat kidneys from oxidative damage. Nephroprotective effects were confirmed by measuring renal DNA damage and ROS production in living kidney cells. Additionally, histological structure was unchanged. Summer savory (Satureja hortensis L. aerial parts) methanolic extract was tested for its ability to reduce cisplatin-induced oxidative damage in testicular,

kidney, and liver tissues (Tatjana Boroja *et al.,* 2018). Ten days following injection, S. methanolic extracts. Wistar rats received 50, 100, and 200 mg/kg hortensis daily. Cisplatin was given intraperitoneally at 7.5 mg/kg body weight on day 5 to induce toxicity. S. In mice killed by cisplatin, hortense extract restored tissue morphology, reduced tissue oxidative stress, and raised serum kidney, liver and testicular function markers. The Bcl-2/Bax ratio was likewise abnormal. UHPLC/DAD/HESI-MS/MS showed that S. The three most abundant phenolic compounds in hortensis extract were rosmarinic acid (24.9 mg/g), caffeic acid (1.28 mg/g), and naringenin (1.06 mg/g). Based on our findings, S. Adding phenolic components from hortensis, such as rosmarinic acid, to pharmaceutical and functional food formulations to promote healthy oxidative stress or treat oxidative damage-related disorders may be helpful. Nearly half of cancer treatments involve cisplatin (Sarfraz Ahmad *et al.,* 2019). The effectiveness is hampered by dosage-dependent adverse effects. *Berberis vulgaris* L. is medicinal. Serves numerous purposes. B. Traditional medicine uses vulgaris. The strong alkaloid berberine was extracted from B.'s methanolic root extract using HPLC. verrucosis (BvRE) measured. By weight, BvRE had 10.29% beberine chloride. Twenty-five healthy male albino Wistar rats weighing 130-180 g were tested for cisplatin-induced hepatotoxicity, hyperlipidemia, and nephrotoxicity to see if BvRE prevents or cures it. Curing or preventing disease studies use one i.p. Nine 500 mg/kg/day oral BvRE doses and four cisplatin doses were given. To assess cisplatin toxicity, organ tissue homogenates (malondialdehyde and catalase biomarkers) and serum (urea, creatinine, total protein, alanine transaminase, aspartate transaminase, total cholesterol, and triglyceride) were biochemically analyzed. A number of metrics showed significant differences ($p < 0.05$). Histological studies of kidney and liver tissues in curative and preventive groups showed that BvRE reduced cisplatin-induced hepatotoxicity, hyperlipidemia, and nephrotoxicity. Additionally, the preventative program showed promise. The tetrazolium (MTT) assay measured the number of viable HeLa cells treated with cisplatin, BvRE, or both. MTT showed that cisplatin and berberine alone were less sensitive to HeLa cells. Combining the two medicines at the same doses dramatically increased HeLa cell growth inhibition. A recent study found BvRE confers cisplatin resistance. Ridzuan *et al.,* (2019) state that cisplatin treats metastatic tumors and advanced bladder cancer. Higher doses may cause nephrotoxicity and other problems. DNA damage from cisplatin kills kidney cells. Neotoxicity often results from oxidative stress. Multiple studies show that ginseng, curcumin, licorice, honey, and pomegranate alleviate oxidative stress by restoring antioxidant enzyme levels and lowering inflammation. Vitamin C, E, and riboflavin-treated cancer patients had lower blood urea and higher kidney antioxidant enzyme levels before cisplatin induction. Due to their antioxidant and anti-inflammatory properties, these natural components can help treat cisplatin-induced nephrotoxicity. To evaluate which traditional medicine constituents reduce cisplatin-induced nephrotoxicity best. Tatjana Jurić *et al*., (2020) found that methanol extracts from *Alchemilla vulgaris* L.'s roots and aerial parts were effective. AVA and AVR were tested to prevent cisplatin-induced testicular and hepatopancreatic damage in mice. A detailed phenolic analysis of AVA and AVR was conducted using UHPLC/DAD/ (−) HESI-MS/MS. The extracts were given orally to male Wistar rats at 50, 100, and 200 mg/kg b.w. create toxicity. During 10 days.... One 7.5 mg/kg b.w. dose was given to rats on day five of cisplatin. Histopathology, serum biochemical indicators of hepatorenal and testicular tissue injury, and oxidative stress were assessed. Cisplatin use, serum oxidative stress, liver, kidney, and testicular damage, and tissue shape changes were reduced by AVA and AVR. Chromatographic analysis revealed over twenty phenolic components in the extracts. The two extracts largely included catechin, ellagic acid, and gallate. The findings imply that *P. vulgaris* may minimize oxidative stress and cisplatin-induced damage during treatment. Cisplatin (Cis) induces dose-dependent renal impairment, according to Esmaeel Panahi kokhdan *et al.,* (2021). *Zataria multiflora* Boiss's defensive properties are studied. Z.M.B., carvacrol, and thymol reduce rat cisplatin-induced nephrotoxicity. The FDA approved platinum-based anticancer drug cisplatin in 1978 due to its efficacy (Norhashima Abd Rashid *et al.,* 2021). Despite treating solid tumors, cisplatin is harmful to several organs, limiting its therapeutic use. The increased formation of reactive oxygen species in cisplatin-induced hepatotoxicity causes oxidative stress, inflammation, DNA damage, and liver apoptosis, which are poorly understood. Flavonoids, terpenoids, polyphenols, phenolic acids, and other substances abundant in oil and plant extracts may reduce inflammation and restore antioxidant enzyme activity, reducing oxidative stress. Honey and royal jelly reduce liver free radicals and serum transaminases after cisplatin. Because of their therapeutic properties, these natural chemicals may substitute cisplatin in treating hepatotoxicity. A lab investigation found that certain natural compounds protect against cisplatin-induced hepatotoxicity. According to Jie Zhou *et al.,* (2022), cisplatin's most common side effect, nephrotoxicity, limits its therapeutic efficiency. Oxidative stress, a hallmark of cisplatin-induced disease, degrades intracellular material. ROS can cause necrosis and apoptosis. Cisplatin kills antioxidant enzymes, consumes endogenous antioxidants, stimulates mitochondrial crosstalk between the endoplasmic reticulum and Ca^{2+} via ROS and Ca^{2+}, and removes the CYP system to produce ROS in cells. This increases ROS and oxidative stress in the cell. Natural antioxidants may reduce cisplatin-induced nephrotoxicity by modulating nonredox pathways and decreasing free radicals. This review provides practical and theoretical information on natural antioxidants and their medical benefits. However, it offers a new perspective on cisplatin nephrotoxicity's complex mechanism, which may aid its treatment. As highlighted by Amany Iskander *et al.,* (2022), cisplatin is commonly utilized to treat many solid cancers. Cisplatin is rarely used in medicine due to its kidney injury risk. Fibrosis, inflammation, and oxidative stress are the major kidney damaging mechanisms of cisplatin. The kidneys' damage from cisplatin is studied using NAD^+-dependent redox enzymes like NAD kinase, CD38, sirtuins, poly-ADP ribosylase polymerase, and NNT. We also investigate if plant-based natural compounds can help these enzymes reduce cisplatin-induced kidney impairment. The usual techniques for producing mice and rat models of cisplatin-induced kidney damage are also described. More research is needed to understand how NAD^+-dependent redox enzymes control cisplatin-induced kidney injury. The literature on natural product protection against cisplatin-induced kidney injury and NAD^+ redox biology is extensive. Oxaliplatin, cisplatin, carboplatin, and ormaplatin treat certain cancers

(Shaloam Dasari *et al.,* 2022). A high percentage of patients return with the disease because to treatment resistance or organ malfunction, including gastrointestinal, hematologic, renal, cardiovascular, and neurological systems. An detailed literature review on therapeutic choices, including combination therapy with natural products, and cisplatin's molecular modes of action allowed us to assess current understanding. Thus, we searched MEDLINE, PubMed, Google Scholar, and others for relevant material. We reviewed research literature on cisplatin, natural products, combination therapy, cancer treatment, therapeutic approaches, and action mechanisms. Our research shows mixed results for new cancer treatments including cisplatin-natural product combos. Many bioactive compounds in medicinal plants have been shown to treat human ailments in labs and living species. This makes them ideal for drug development. Natural ingredients boost cisplatin's efficacy and toxicity, according to preclinical research. Natural products modulate MAPK and p53 signal transduction pathways to boost cisplatin's chemosensitivity and cell death, according to extensive studies. Natural products modulate gene transcription factors and reduce cell death and necrosis to protect organs against cisplatin. Several cisplatin formulations delay drug release, reduce systemic toxicity, and increase half-life using polymeric, inorganic, carbon, and lipid nano-drug delivery methods. Nanocapsules, hydrogels, and nanogels let cells penetrate, target cancer cells, and prevent tumor growth.

Materal methods

Leaves of medicinal plants from Chhattisgarh were evaluated for their ethno-medicinal anti-cancer properties. *Aegle marmelos* (Bael) was selected as the plant. The leaves of the above plants were extracted using aqueous and ethanolic/hydroethanolic solvents; alcoholic extracts gave higher yields. In vitro qualitative phytochemical analysis of each leaf extract identified the following compounds: phytosterols, saponins, phenolic compounds, flavonoids, alkaloids and terpenoids. However, the presence of vitamin C was particularly identified in amla and kadam leaves. Based on the findings of quantitative analysis involving phenols, flavonoids, flavonols and vitamin C, it was observed that AET displayed the highest significant phenolic concentration (396.00 ± 0.0 µg/mg), followed by KET, BET, KAQ, MET and MAQ. The flavonoid content in the leaf extracts varied between 62.20±2.42 and 13.27±0.12, with KET and AET having the highest values. The sample labeled as MET displayed the most significant flavonol concentration, followed by AET, BET, AAQ, BAQ, KAQ and KET. In contrast, the samples with the highest documented concentrations of vitamin C were AET (348µg/mg) and AAQ (140µg/mg), respectively. The concentration of phytochemicals in the alcoholic extracts was found to be significantly higher than their corresponding aqueous extracts; indicating that alcoholic solvents are more easily extractable. The leaf extracts exhibited clear peaks in the UV-Vis spectroscopy range of 200-350 nm, which were found to be associated mainly with flavonoids and phenolic compounds. Moreover, the FTIR spectra of each leaf extract revealed the presence of carboxylic acids, carbohydrates, phenolics, flavonoids, amides and other functional groups. These findings further confirmed the previously reported phytochemical observations. The above phytochemicals were further validated through GC-HRMS analysis of the leaf extracts.

Result and Discussion

Medicinal plants contain many compounds with pharmacological properties that can be used to develop new, effective treatments for many diseases, including kidney problems, and to reduce or eliminate the toxic effects of many drugs. Cisplatin is widely used to treat many cancers, although nephrotoxicity is its biggest downside. Several natural and manmade substances protect against cisplatin-induced nephrotoxicity. However, early results and practical evaluation did not match, preventing clinical use of the reported drugs. Cancer biology needs a novel cisplatin treatment that prevents nephrotoxicity. This study examines how Chhattisgarh medicinal herbs protect against cisplatin-induced nephrotoxicity. These plants have been shown to fight cancer. According to scholarly literature [Ritesh and Sanmati 2010], 33 medicinal plants from Chhattisgarh, India, show anti-cancer activities in vitro and in vivo. Four of the above therapeutic plants' leaves *Aegle marmelos* were chosen for this study due to ethnobotanical value. Aqueous and ethanolic/hydro-ethanolic leaf extracts of the aforesaid medicinal plants were analyzed for phytochemicals and antioxidant activity. An in vivo investigation examined whether the leaf extract with the highest antioxidant activity may protect against cisplatin-induced nephrotoxicity. The active fractions are chemically determined by column chromatography after fractionating the selected extracts. Since phytochemical concentrations vary with leaf age, mature leaves of the required plants were collected first. Mature leaves have more phytochemicals than young or old ones. Extraction is the main method for extracting bioactive phytochemicals from plants. However, many factors affect extraction efficiency. Sample-to-solvent volume ratio, solvent polarity, extraction method, extraction duration, particle size, phytochemical properties, solution pH and temperature, and sample-to-solvent ratio affect the extraction process. This study used aqueous and ethanolic/hydro-ethanolic solvents for extraction. Higher yields were obtained using hydroethanolic extraction. These solvents are crucial for polar chemical extraction [Stalicas, 2007]. According to Chatha et al. (2006), alcoholic and hydro-alcoholic extracts have higher extraction values than aqueous extracts. Phytochemical analysis of the leaf extracts revealed phenolic chemicals, flavonoids, alkaloids, terpenoids, saponins, and phytosterols. The phytochemicals above inhibit cancer, diabetes, and inflammation (Hamzah et al. 2013; Nagwani et al. 2010). Quantifying phenolics, flavonoids, flavonols, and vitamin C was also done. The total phenolic content was calculated using the Folin-Ciocalteu (FC) technique. The study found that AET had the highest phenolic content (396.00 ± 0.0 µg/mg), followed by KET, KAQ, BET, BAQ, MET, and MAQ. The leaf extracts above have a higher phenolic content than leaves of other medicinal plants [Chaudhary and Swarnkar, 2011; Song *et al.,* 2010; Kolli *et al.,* 2015; Camarena-Tello, 2018]. Each leaf treated with alcoholic extracts contained considerably more phenolics.

Ethanolic extracts may have more phenolic groups or generate a phenolic complex that is soluble in alcoholic solvents. Flavonoid content was KET > AET > KAQ > AAQ > BET > MET > MAQ > BAQ. Leaf extracts had higher flavonoid concentration than other therapeutic botanical species (Choudhary and Swarnkar, 2011; Mahmoodi *et al.,* 2016). Solvent application had similar effects on flavonoid and phenolic contents of each extract. The detected flavonol concentrations were: MET > AET > Bet > AAQ > BAQ >

KAQ > KET. AET and AAQ had the most vitamin C. Vitamins A, E, and C account for 80% of plant antioxidant action, according to research. In early UV-Vis spectral examination of leaf extracts, 200-350 nanometer peaks were found. The classification is rich in phenolic and flavonoid chemicals. UV-Vis spectral analysis confirmed that each leaf extract contains phenols and flavonoids. All leaf extracts contained phenolics, flavonoids, carboxylic acids, carbohydrates, amides, and other chemicals, according to GC-HRMS analysis. This research also confirmed the functional groups in all leaf extract FTIR spectra. These phytochemicals have high antioxidant activities, which explain their diverse pharmacological effects. The aqueous and alcoholic leaf extracts have different functional groups than the alcoholic extract, which solely has O–H. The OH group's hydrogen bonding may explain the ethanolic extract's increased antioxidant activity. The chemical structures of phytochemicals in the leaves of the above plants affect their antioxidant ability. Each extract's antioxidant activity was measured in vitro using the DPPH free radical scavenging test. While ascorbic acid was the positive control, AET and AAQ had the lowest IC50 values. Other researchers have found comparable IC50 values for different leaf species [Akhtar and Mirza, 2015; Chen *et al.,* 2017]. The significant Pearson connection between DPPH radical scavenging activities and TPC and TFC of leaf extracts suggests that the interaction of ABTS and potassium persulfate produces a blue-green stable ABTS radical cation to test the efficacy of ABTS radical catalysis in removing free radicals. After the stable ABTS radical cation forms, antioxidant chemicals cause colorlessness and decreased absorption at 600nm, according to Sanchez-Moreno (2002). This impact is due to the chemicals' antioxidant action. The plant extracts have IC50 values for ABTS radicals ranging from 18.24 ± 3.9 to 155.88 ± 9.0. Lower IC_{50} values were found in BAQ, KET, and AET solutions. Note that the IC_{50} values of the extracts given above do not differ significantly ($P < 0.05$) from those of ordinary tannic acid. Flavonoids, phenolics, and vitamin C caused the radical scavenging activity of antioxidants in all leaf extracts, as evaluated by ABTS, according to the Pearson correlation coefficient. In addition, the leaf extracts employed in this investigation had much lower IC50 values than other leaves (Dzoyem & Eloff, 2015). The FRAP assay [Benzie & Szeto, 1999; Shahidi & Zhong, 2015] measures antioxidant activity by forming a blue Fe^{2+} ligand complex through single electron transfer, reducing Fe^{3+} ions in an acidic environment.

AET was chosen as the highest FRAP leaf extract. Total flavonoid concentration and FRAP value correlated more strongly on the Pearson correlation graph than FRAP value and TPC vitamin C content. More study shows that conjugated double bonds in phenolic substances such hydroxyl groups, flavonoid compounds, and vitamin E are necessary for antioxidant FRAP activity [Pieta, 2000; Muller *et al.,* 2011]. Antioxidants reduce Mo (VI) to Mo(V) in the phosphomolybdate experiment to measure antioxidant activity. According to the phosphomolybdate experiment, KET and AET had the strongest antioxidant activity. This antioxidant activity assay matches the Pearson correlation between the total flavonoid content of all leaf extracts and the phosphomolybdate assay. TFC correlated most with TPC, TFC, and vitamin C.

The reducing power of an extract or molecule is a key antioxidant activity indicator. This test uses a single electron transfer technique to convert a yellow Fe3+/ferricyanide complex to a blue Fe2+/ferrous state and produce a green complex with antioxidant chemicals (Dave, 2009). AAQ and AET leaf extracts reduced the most again. The Pearson correlation coefficient between total reducing power, flavonoids, vitamins, TFC, and TPC was highest with TPC ($p = 0.99$), followed by TFC and vitamin C. This suggests that phenolic chemicals dominate the reducing capacity of the aforesaid leaf extracts, followed by vitamins and flavonoids. Compare the current leaves to others; they reduce better (Akhtar and Mirza, 2015). The variation in antioxidant values shows that each method analyzes a distinct component of antioxidant capability. The single electron transfer method is employed in phosphomolybdate, FRAP, and total reducing power assays (Badrinath *et al.,* 2010). However, DPPH and ABTS combine hydrogen and single electron transport. The hydro-ethanolic leaf extract of *Emblica officinalis* (AET) had the highest antioxidant capacity in all leaf extract studies. Quantitative and spectral tests confirmed that the extracts' high phenolic and vitamin component concentrations caused the problem. Next, extracts are chosen for further study. Alcohol leaf extracts from all four medicinal plants were tested in vitro against three human cancer cell lines for anti-cancer activities. A498; SK-OV-3; and T-24 have modest anti-cancer activity. However, AET showed some antiproliferative action in each cell line, although not statistically significant. Gallic acid from Phyllanthus emblica leaves inhibits BEL-7404 human hepatocellular carcinoma cell proliferation [Huang and Zhong, 2011]. This suggests E. coli fights cancer. Other cell types may benefit from C's anticancer capabilities. officinalis. Cisplatin is effective against a wide range of solid cancers when given alone or in combination. This medicine is administered worldwide despite dose- and duration-dependent renal tissue side effects. Due to the above mechanisms, oxidative stress is the main cause of renal toxicity. Combining cisplatin with an agent with anti-cancer, anti-inflammatory, and cell-protective properties, as well as antioxidant compounds that reduce oxidative stress in renal tissue, may reduce its cytotoxic effects.

Previous research have shown that amla leaf polyphenols are anti-diabetic, anti-carcinogenic, and anti-oxidant. Additionally, these phytochemicals reduce oxidative stress [Nain *et al.,* 2012a; Asmawi *et al.,* 1993; Moilanen 1997; Nain 2012b]. The hydro-ethanolic leaf extract of *Emblica officinalis* had the highest antioxidant capacity in this investigation. *Emblica officinalis* hydro-ethanolic leaf extract reduces cisplatin-induced nephrotoxicity.

Male Wistar rats were used to test a hydro-ethanolic leaf extract of *Emblica officinalis* against cisplatin-induced nephrotoxicity. The rats were assigned to control rats (vehicle and control rats), cisplatin-treated rats, and leather rats treated with cisplatin at 12, 200, and 300 mg/kg BW, and leather rats treated at 100, 200, and 300 mg/kg BW. The animals were sacrificed on the fourteenth day after receiving cisplatin and leaf extracts for thirteen days. Leaf extract dosage is based on a previous acute toxicity study on the same extract (Nain *et al.,* 2012b).

In contrast, this study used 12 mg/kg BW cisplatin [Sandeep & Krishnan, 2010]. However, rodents showed nephrotoxicity three days after receiving cisplatin injections over 5 mg/kg BW (DeWoskin & Riviere 1992; Babu *et al.,* 1995). Numerous researches suggest greater cisplatin doses for nephroprotection. Increasing the dosage may cause harmful

consequences, but it creates a better setting for testing the test compound's protective benefits. Clinical practice uses 16 mg/kg BW, up from 12 mg/kg BW [Somani *et al.,* 2000]. The study found unchanged hydroethanolic leaf extracts of E. Officinalis prevented rodent cisplatin-induced nephrotoxicity.

The normal BUN and creatinine levels in leaf extract-fed animals corroborate this claim. Creatinine and BUN are renal function biomarkers. A single dose of cisplatin (12 mg/kg BW) significantly raised creatinine and BUN, which indicate renal dysfunction, compared to the vehicle control group, the normal group, and the normal and normal groups. More research has shown that cisplatin-treated animals have higher creatinine levels due to elevated GAMT levels [Hung *et al.*, 2007]. The current study found E's protective effects, as did Malik *et al.,* (2016). Were also seen the cisplatin nephrotoxicity resistance of officinalis fruit extract was assessed. One dose of cisplatin (12 mg/kg BW) induced considerable weight loss and an increase in relative kidney weight from day one to day fourteen. Treatment includes E. Officinalis leaf extracts at 100 mg/kg and 200 mg/kg BW significantly reduced relative kidney weight and increased body weight. However, Table 4.10 shows that larger concentrations did not impact the above parameters. Previous studies have shown similar weight loss (Sahu *et al.,* 2013; Naghizadeh, 2010). Cisplatin-induced weight loss may be due to gastrointestinal toxicity and decreased eating. Cisplatin causes kidney damage by releasing reactive oxygen species (ROS), inducing non-enzymatic antioxidant defense, and decreasing antioxidant enzyme activity.

Thus, non-enzymatic marker concentrations and antioxidant enzyme activity were measured. According to data, a group of mice given a single dosage of 12 mg/kg BW cisplatin had considerably lower SOD, CAT, GPx, and GR than the control group. Lipid peroxidation increased in the cisplatin group. According to previous research, cisplatin causes a nephrotoxic reaction in renal tissue, characterized by reactive oxygen species generation and reduced enzymatic and non-enzymatic antioxidant defense mechanisms. Naghizadeh (2010), Pillai (2011), Naziroglu (2004).

Cisplatin damages the mitochondrial respiratory chain in renal tubular cells, increasing ROS generation, particularly superoxide anions (O2...-) and H2O2. SOD, CAT, GPx, and GR activity in rat renal tissues is also reduced. H2O is formed by partial reduction with transition metals like iron and superoxide anion. Dos Santos et al. (2012) found that hydroxyl radicals interact with proteins, lipids, and DNA to damage genomic stability, cell integrity, and enzyme activity. Treatment includes E. Officinalis leaf extract significantly increased rodent antioxidant enzyme activity. E's minimal concentrations (100 mg/kg and 200 mg/kg) are noteworthy. Cisplatin's nephrotoxic effects were prevented by Origanum officinalis leaf extract, which also boosted enzymatic activity in all species.

Despite 400 mg/kg BW leaf extract administration, Catalase activity did not increase. Later studies found that CAT activity was more vulnerable to acute renal damage from cisplatin than SOD/GPx/GR activity [Lee *et al.,* 2013]. The current study found that leaf extract affected GPx activity more than other enzymes. In the cisplatin group, renal MDA, an indication of lipid peroxidation, increased significantly. Reduced SOD and CAT activity may explain cisplatin-induced lipid peroxidation in animals. In groups that received leaf extract at 100, 200, and 400 mg/kg BW, MDA levels were normal. E is hypothesized. Serves as protection. An extract from Officinalis leaves may reduce oxidative stress by boosting enzymatic antioxidants. This investigation confirms previous findings (Sandeep *et al.,* 2010; Abdel *et al.,* 2014; Saad *et al.,* 2002; Somani, 2000).

The vehicle control group, normal control group, and leaf extract group had typical kidney tissue histopathologically. In contrast, cisplatin-treated patients had renal tubule and glomerulus damage. Previous investigations [Pillai *et al.,* 2011; Abdel *et al.,* 2014; Sharma & Goyal 2012] support this result. After 13 days of leaf extract treatment, mice' histological analysis showed that many tubules were in decline, indicating that the damage was not completely eliminated. The group that received leaf extracts at 100 mg/kg and 200 mg/kg had the least injury of the three regimens, supporting the biochemical parameters studied in the research. Cisplatin can also cause anemia, especially in multiple-dose administrations. Myelosuppression, which reduces serum levels, may be the cause. One study found membrane injury in chicken red blood cells exposed to cisplatin [Kutwin *et al.,* 2014]. Red blood cell morphological alterations and hemolysis were observed in rats treated with cisplatin. Hydroethanolic unrefined leaf extract of E. An additional fractionation of officinalis was conducted in order to obtain the active fraction or compound via silica gel column chromatography. Following UV-Vis spectral analysis of each tube fractionated by column chromatography, it was possible to identify seven distinct fractions. Fractions 1, 3, and 7 exhibited either solitary or double peaks among the seven. As a result, the antioxidant activity exhibited by these fractions serves as an additional screening criterion. Fifth of the fractions that were referenced exhibited the smallest IC50 value in terms of DPPH radical scavenging activity. Similarly, fractions 3 and 1 occurred. As a result, additional GC-HRMS analysis is conducted on fractions 3 and 7 to determine the active compounds and purity. When it comes to the identification of compounds, gas chromatography coupled with high-resolution mass spectrometry is the method most frequently employed. From the five peaks in fraction 3's GC-HRMS spectrum, phenol 2, 4-bis [1,1-dimethyl ethyl] (RT-9.57) and di-α-Tocopherol (vitamin E) (RT-25.23) were determined to be the most significant compounds. The leftover peaks are aliphatic hydrocarbons and carboxylic acids. Antioxidants include vitamin E and phenolics.

Vitamin E and phenol found in fraction 3 may explain its antioxidant properties. GC-HRMS also detected vitamin E in diluted hydroethanolic E extracts. Propaedium arborealimaris. A peak at RT 22.69 in Fraction 7's GC-HRMS spectra was identified as 1, 2-Benzene dicarboxylic acid, di-isooctyl ester (phthalic acid) by searching the NIST library. The 50% phallic acid concentration was confirmed by 1H NMR and FTIR. Fractions 3 and 7 were further tested for in vitro anticancer activity against three human cancer cell lines—A498, SK-OV-3, and T-24—using the SRB assay. Adriamycin was a positive control. Additionally, the MTT experiment was performed on MDA-MB-231 and MDA-MB-468 triple negative breast cancer cell lines using cisplatin as the reference chemical. Fractions 3 and 7 (GI50>80) and the parent crude extract AET did not impede A498, SK-OV-3, or T-24 cell proliferation.

Crisplatin, fractions 3 and 7, and AET inhibit MDA-MB-231 and MDA-MB-468 TNBC cell growth. Additionally, caspase 3 immunofluorescence in MDA-MB-231 cells showed that

fractions 3 and 7 triggered cellular death, similar to cisplatin. Most laboratory experiments use MDA-MB-231 and MDA-MB-468 breast cancer cell lines. Epithelial breast cancer cell lines were acquired from a 51-year-old Caucasian lady with metastatic adenocarcinoma via pleural effusion. In contrast to breast cancer tumors, triple negative breast cancer cell lines consistently display prognostic markers like progesterone receptors (ER), HER-2/Neu amplification, and PR. In contrast, triple negative breast cancer cell lines lack the receptors listed above. Treatments that target malignancies with the above receptors fail against tumors without them. Thus, TNBC treatments must improve.

Fraction 3 contained phenol 2, 4-bis [1, 1-dimethyl ethyl] and tocopherol. Fraction 7 contained phthalic acid (1, 2-benzene di-carboxylic acid, di-isooctyl ester). Currently, there are few data on the inhibitory effects of α-tocopherol on cell viability in other cell lines. However, its analogues show antiproliferative properties (McLntyre *et al.,* 2000). Several other researches have shown that plant-based phenolic extracts and polyphenols, including as anthocyanins, kaempferol, quercetin, coumaric acid esters, and ellagic acid, have specific anticancer activities. Conversely, cell lines perceive affects differently depending on exposure length and dosage (Dai & Mumper, 2010; Zhang *et al.,* 2008). Kampa *et al.,* (2004) also found that caffeic, syringic, sinapic, protocatechuic, ferulic, and 3, 4-dihydroxyphenylacetic acids inhibited T47D human breast cancer cell growth. The inhibitory impact varied with dosage and time. Unlike ordinary phenols, phospholic acids and polyphenols suppress growth. No anticancer studies have been published on phthalic acid (1, 2-Benzenedicarboxylic acid, diisooctyl ester). Despite this, Lee et al. (2000) found that phthalic acid derivatives inhibited sarcoma 180 tumor cell growths in rats. The HEK 293 normal kidney cell line was used to test the toxicity of AET crude extract, fractions 3, and 7. Assay results showed that neither fractions nor crude extract were cytotoxic to control cells. Fractions and crude extract are nephroprotective, but the crude extract selects against proliferation. Combining the present extract with cisplatin to reduce renal damage may be beneficial.

Recommendations- Conducting an evaluation of the protective properties of extracts derived from medicinal plants against cisplatin-induced toxicity is a critical endeavor in the domains of pharmacology and medical research. Constantly administered cisplatin, a chemotherapy drug, frequently induces serious adverse effects, including neurotoxicity and nephrotoxicity, that reduce its clinical utility. By conducting an inquiry into the potential of medicinal plant extracts to mitigate these adverse effects, researchers may uncover supplementary or alternative therapies that enhance the efficacy of cisplatin while reducing its toxicity. Through the utilization of rigorous evaluation methods including in vitro and in vivo experiments, biochemical assays, and animal models, researchers are capable of identifying potentially advantageous plant extracts that exhibit protective characteristics against cisplatin-induced toxicity. The findings of this research present substantial promise for the development of novel therapeutic strategies that improve the quality of life and likelihood of survival for cancer patients undergoing medical intervention.

Limitation of the study- While the investigation into the potential protective properties of medicinal plant extracts against cisplatin-induced toxicity provides noteworthy advancements, it is not without limitations. To commence, an exclusive reliance on in vitro models may not adequately capture the complexities of physiological responses and interactions that take place in vivo. The generalizability of the study may have been further compromised due to the specific concentrations employed and the restricted range of medicinal plants investigated. Furthermore, variations in the results of the experiments might result from disparate extraction methodologies and plant provenances. Moreover, potential adverse interactions or synergistic effects with other commonly prescribed medications might be overlooked in the evaluation of cisplatin's protective effects. In summary, it is advisable to exercise prudence when extrapolating these findings to clinical settings involving humans; further preclinical and clinical investigation is necessary to comprehensively ascertain the safety and efficacy of these botanical extracts.

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