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Renal Protective Efficacy of *Terminalia chebula, Terminalia bellirica, Phyllanthus emblica* and their Formulation as Triphala on Imidacloprid Induced Renal Toxicity by Histopathological and Biochemical Parameters

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Abstract: *Effect of Imidacloprid induced renal damage and its amelioration was carried out at definite time periods in different groups for 28days and experimented. Biochemically evaluated with renal markers it showed elevated level of urea, uric acid, creatinine, sodium and decreased in potassium the mineral element. Administration of Imidacloprid produced, renal tubules congestion, mild vacuolar degeneration, edema in Bowman's capsule (40mg/kg/b.w), disintegration of Bowman's capsule, dilation of capillary tubules, renal tubule congestion, vacuolar degenerations were observed in (80mg/kg/b.w). Animals were treated with Terminalia chebula, Terminalia bellirica, Phyllanthus emblica and their formulation called Triphala (1:1:1) drug. Phyllanthus emblica has shown extraordinary effect of renal protective role comparing the four samples which was proved virtually.*

Keywords: *Histopathology, Imidacloprid, Triphala, Renal protective*

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I. Introduction

Kidney is a target organ for wide variety of toxic agents as it acts as a blood filter during the excretory process. As kidneys receive high blood flow, the insecticides might be delivered to these organs in relatively high amounts through systemic blood circulation. Glomerulus reabsorbs salt and water, the chemical which was found in the renal tubules may interrupt the biochemical constituents and histology of kidneys in test animals [1]. Nephrotoxicity is one of the most common kidney problems and occurs when body is exposed to a drug or toxin [2]. Number of therapeutic agents can adversely affect the kidney resulting in acute renal failure, chronic interstitial nephritis and nephritic syndrome because there is an increasing number of potent therapeutic drugs like aminoglycosides antibiotics, NSAID's, chemotherapeutic agents [3]**.**

The term renal failure primarily denotes failure of the excretory function of kidney, leading to retention of nitrogenous waste products of metabolism in the blood [4]. There is a failure of regulation of fluid and electrolyte balance along with endocrine dysfunction. The renal failure is fundamentally categorized into acute and chronic renal failure [5]. Nephrotoxic injury is damage to one or both of the kidneys that results from exposure to a toxic material usually through ingestion, nephrotoxic injury can lead to acute renal failure. In which kidneys suddenly lose their ability to function or chronic renal failure, in which kidney function slowly deteriorates [6].

Imidacloprid is a neonicotinoid insecticide which has become an important pest control agent on many crops. The neonicotinoid insecticides are related to nicotine in their structure and action at the nicotinic acetyl choline receptor. The history of neonicotinoids can be traced to the late 1970s when chemists at shell investigated the heterocyclic nitro-methylenes as potential insecticides [7]**.**

Human health risks vary with the type of the pesticides and also with the extent of vulnerability. Immediate human health hazards from pesticides include mild headaches, flu, skin rashes, blurred vision and other neurological disorders and rarely paralysis, blindness and even death. Long run health impacts include cancer, infertility, miscarriage, male sterility, birth defects and effects on the nervous system [8]**.**

Toxicological studies of imidacloprid are limited but they have shown mild pathological changes in the brain, kidney and liver of exposed rats [9]. Imidacloprid acts in insects at the nAChRs, suggesting that this may

also be targeted in mammals. Patients with clinical toxicity due to exposure of Imidacloprid in a deliberate suicide attempt [10].

Kidneys of test rats revealed marked tubular dilation, hydropic degeneration in tubular epithelium, moderate congestion and haemorrhage in the cortex and medulla during fenitrothion treatment [11]. Nephrotoxicity of pesticides has been reported in mice [12] [13]**.** Imidacloprid is a systemic, chloro nicotinyl insecticide, due to its acute toxicity, imidacloprid become one of the most widely used insecticides in the world [14].

II. Materials And Methods

2.1 Sample Collection and authentication

Fresh fruits of *Terminalia chebula Retz.*,*Terminalia bellirica Roxb.* and *Phyllanthus emblica L.* were collected from hill areas, Atthipattu (Thiruvannamalai), Therambattu (Vellore) and Sirumalai (Dindugal). The samples were identified and authenticated by Dr. John Britto, Rapinet Herbarium, St. Joseph's College, Trichy, Tamilnadu, India and given the Voucher Specimen No.VEA/001/2013, VEA/002/2013 and VEA/003/2013 respectively**.**

2.2 Extraction

500gm fruits of *Terminalia chebula*, *Terminalia bellirica and Phyllanthus emblica* were shade dried, pericarp and mesocarp of fruits were pulverized into fine powder individually and formulated in 1:1:1 ratio using a stainless steel blender. Extracts were prepared by using Soxhlet extractor and 95% Methanol were used as solvent, the residue was filtered and concentrated under reduced pressure by rotary evaporator. The final extracts were stored in closed containers until further analysis [15][16].

2.3 Experimental animals

Female albino wistar rats were selected as experimental animals between 6-8 weeks weighing and 160-180grams were procured from Central Animal Facility, SASTRA University, Thanjavur, Tamilnadu, India. Rats were housed in solid bottom polypropylene cages, three rats per cage. Autoclaved rice husk was used as the bedding material and it was changed once in 3 days. The animals were maintained in the animal house sustained temperature at 22 ± 2˚C and humidity 30-70% with light/dark cycle for 12 hours. The experiments were carried out as per the guidelines of (CPCSEA), New Delhi, India and approved by the (IAEC), SASTRA University (Approval Number: 302/SASTRA/IAEC/RPP dated 29.04.2014).

2.4 Histopathological studies

For histopathological study the fresh kidney tissues were collected and immediately fixed in 10% formalin, dehydrated in gradual ethanol (50-100% v/v) cleared in xylene by tissue processor (Leica TP 1020, made in Jerman) and embedded in paraffin. The paraffin embedding technique (Leica EG 1150C) was carried out; sectioned with microtome (Leica RM2125 RTS) at 5µm thickness and stained with hematoxylin eosin dye by automatic staining (Leica ST 4040). Photographic microscopical studies were observed by Trinocular microscope (Nikon, Digital Sight DS-Fi2, made in Japan).

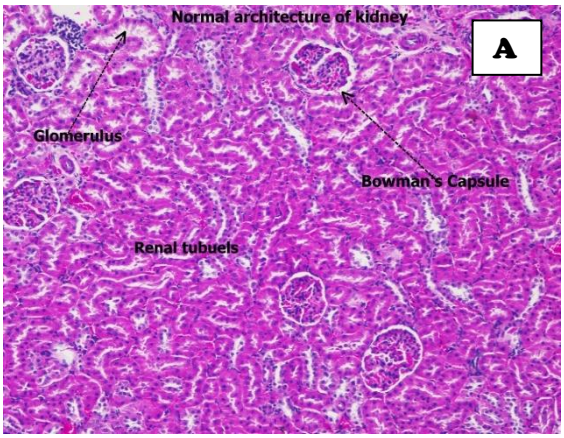
III. Results

Table: 1 Effect of oral treatment of selected herbals on Imidacloprid insecticide induced toxicity in Albino Wistar Rats

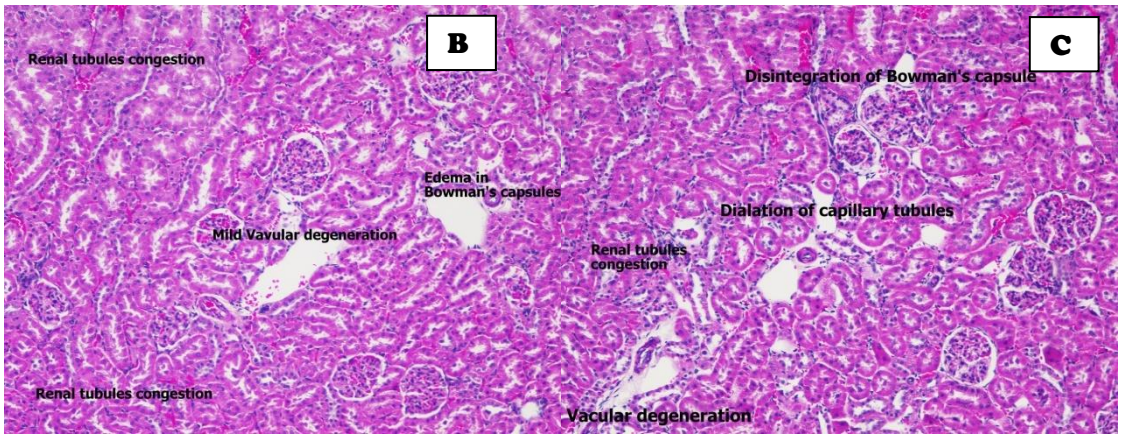
Parameters & Grouping	Urea (mg/dl)	Uric Acid (mg/dl)	Creatinine (mg/dl)	Sodium (mEq/L)	Potassium (mEq/L)
Control	30.00±3.67 ^{a}	5.83±0.75 ^{a}	0.92±0.05 ^{a}	142.50±4.51 ^{a}	5.35±0.22 ^{a}
IMI (40mg/kg)	45.17±0.41 ^{b}	11.47±0.40 ^{b}	1.21±0.02 ^{b}	168.50±2.43 ^{b}	4.50±0.25 ^{b}
IMI (80mg/kg)	51.00±3.67 ^{c}	12.70±0.22 ^{ce}	1.29±0.02 ^{c}	178.17±3.31 ^{c}	4.12±0.10 ^{c}
IMI (40mg/kg)+ *T. chebula*	35.17±1.60 ^{df}	8.18±0.17 ^{de}	1.02±0.04 ^{df}	149.50±5.58 ^{df}	5.27±0.25 ^{a}
IMI (80mg/kg)+ *T. chebula*	39.04±1.79 ^{e}	9.14±0.23 ^{e}	1.08±0.03 ^{de}	157.33±3.98 ^{e}	4.92±0.12 ^{d}
IMI (40mg/kg)+ *T.bellirica*	35.25±3.39 ^{df}	7.00±0.63 ^{ad}	1.04±0.04 ^{df}	145.50±2.66 ^{ad}	5.21±0.17 ^{a}
IMI (80mg/kg)+ *T.bellirica*	38.90±2.10 ^{e}	8.50±0.55 ^{de}	1.11±0.02 ^{ef}	154.50±2.95 ^{e}	4.99±0.03 ^{ad}
IMI (40mg/kg)+ *P.emblica*	34.00±1.67 ^{d}	6.43±0.41 ^{a}	0.99±0.03 ^{ad}	145.38±2.94 ^{ad}	5.43±0.08 ^{a}
IMI (80mg/kg)+ *P.emblica*	37.50±2.32 ^{ef}	8.33±1.03 ^{de}	1.07±0.04 ^{df}	150.17±4.07 ^{f}	5.11±0.12 ^{ad}
IMI (40mg/kg) + Triphala	33.75±2.46 ^{d}	6.24±0.35 ^{a}	0.97±0.03 ^{a}	144.33±3.33 ^{a}	5.45±0.18 ^{a}
IMI (80mg/kg) + Triphala	35.33±0.82 ^{df}	7.23±0.36 ^{ad}	1.04±0.03 ^{adf}	149.83±1.72 ^{df}	18.33±0.26 ^{e}

Values are expressed as Mean ± SD for six rats

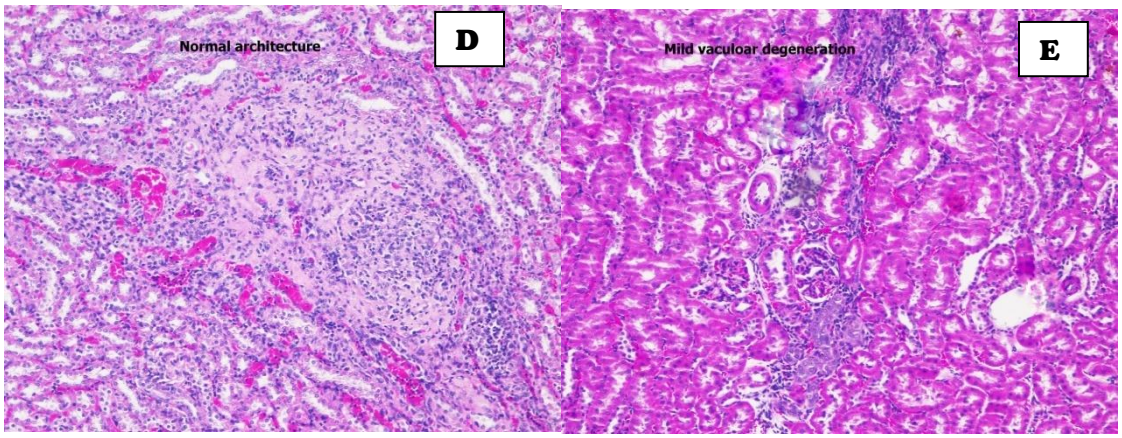
Mean values within the row followed by different letters (Superscript) are significantly ($P< 0.05$) different from each other and same letter are non-significant were comparison by Duncan's multiple range test (DMRT).



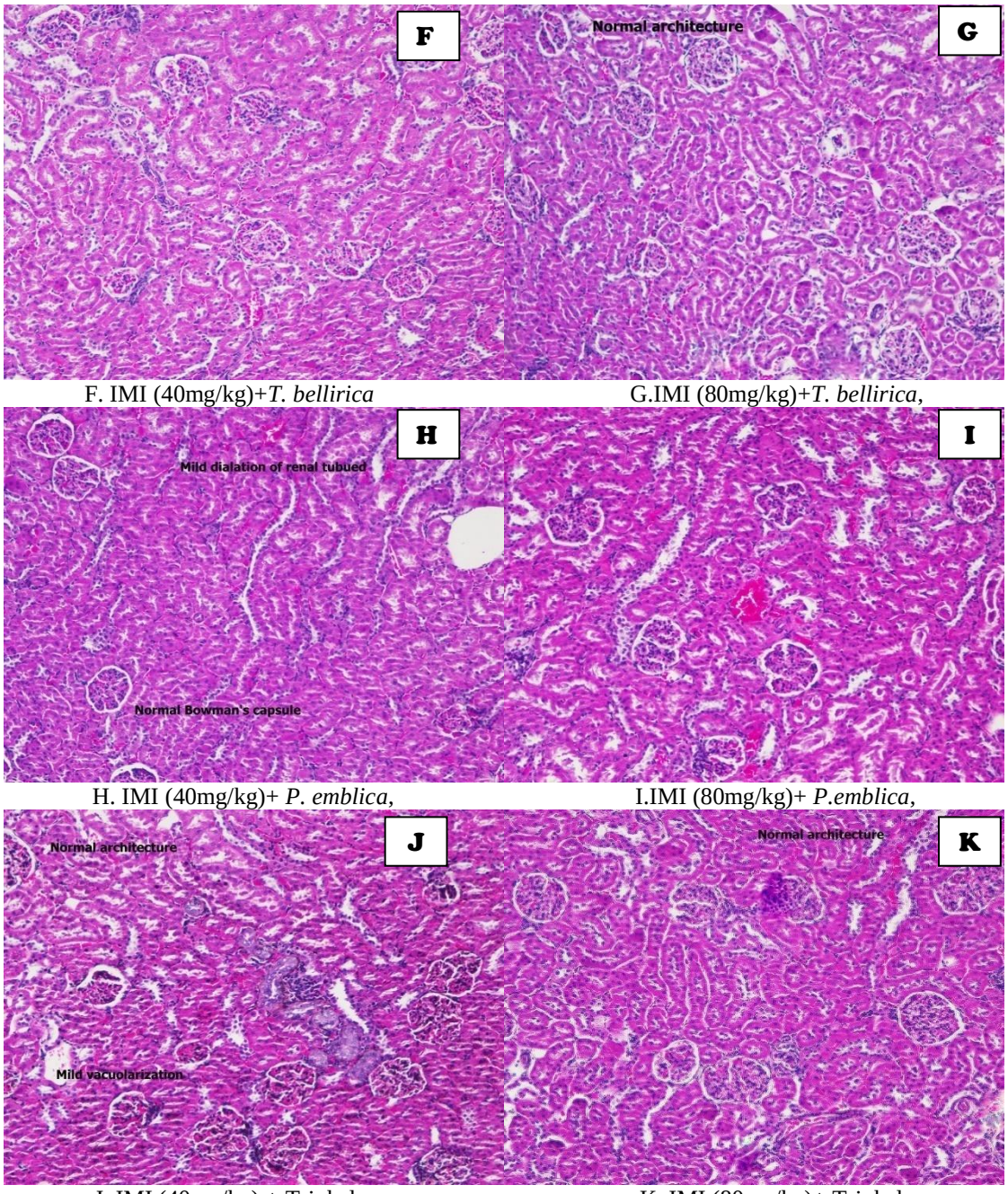
A. Control,



B. IMI –Disease control (40mg/kg), C. IMI –Disease control (80mg/kg),



D.IMI (40mg/kg)+*T. chebula*, E.IMI (80mg/kg)+*T. chebula*,



F. IMI (40mg/kg)+*T. bellirica* G.IMI (80mg/kg)+*T. bellirica*,

H. IMI (40mg/kg)+ *P. emblica*, I.IMI (80mg/kg)+ *P.emblica*,

J. IMI (40mg/kg) + Triphala, K. IMI (80mg/kg)+ Triphala

Fig.1 Histopathological Examination of Kidney tissue section in control and Experimental rats (Hematoxylin & Eosin, 10X)

IV. Discussion

Nephro protective agents are the substances which possess protective activity against nephro toxicity. Oral administration of imidacloprid at the rate of 80mg/kg b.wt for 28 days in male rats resulted in nephro toxicity which was evident from significantly increased serum creatinine levels in Imidacloprid treated rats whereas co-treatment with vitamin C brought mild to moderate improvement in creatinine levels [17]. Drug-induced nephrotoxicity is a common side effect of many therapeutic drugs. Cases of acute renal injury have been increasingly reported over the last two decades and cause morbidity and mortality among patients [18].

The antioxidant rich herbal formulation is used in the treatment of several conditions like jaundice, asthma, constipation, fever, fatigue, anaemia, vomiting, typhoid, chronic ulcers, obesity and eye diseases as well as in the treatment of infectious diseases such as tuberculosis, pneumonia and acquired immune deficiency syndrome [19]. Triphala and its components have diverse medicinal properties and have been shown to possess antibacterial, antifungal, antimalarial, antiviral, anticancer, anti-inflammatory, antioxidant, hepatoprotective and gastroprotective activity [20]**.**

Administration of Imidacloprid produced liver degeneration such as cytoplasmic vacuolation, mild vacuolar degeneration, mild hepatic damage (40mg/kg/b.w) and appearance of blood streaks, hepatic damage and severe vacuolar degenerations were observed (80mg/kg/b.w) and these damages were resolved by the treatment of *Terminalia chebula, Terminalia bellirica, Phyllanthus emblica* and formulated drug Triphala [21]. The findings are complementary with mild focal necrosis of the liver and hepatocellular damage following a subchronic imidacloprid exposure in female rats. Traditional uses of *Terminalia chebula, Terminalia bellirica, Phyllanthus emblica* as well as Triphala but also provide benefit in neurodegenerative diseases or other disorders which oxidative stress and inflammation is implicated [22]**.**

Medicinal plants have curative properties due to the presence of various complex medicinal substances [23]**.** Co-administration of various medicinal plants possessed nephroprotective activity along with different nephrotoxic agents which may attenuate its toxicity. Studies of the metabolites of neonicotinoids have shown that they can be bioactive and act as nAChR agonists or cause secondary toxicity in mammals [24]**.** Administration of *Terminalia chebula* aqueous extract protect the kidney function from Cd intoxication as indicated by significant restoration of serum urea, uric acid, creatinine as well as creatinine clearance levels [25]**.** *Terminalia chebula* protect nickel induced oxidative damage and proved nephrotoxicity and hepatotoxicity through its antioxidant capacity [26]**.**

Lower values of serum sodium indicated inability of kidney to conserve sodium and chloride. Haemodilution too may be involved in the fall of sodium value via excess of water intake and or increased production of endogenous water. Increase of potassium may be due to reduced excretion of potassium aggravated by leakage of intracellular potassium into blood stream as a result of gentamicin induced lesions in renal tubular epithelium, the present results are in harmony with the data obtained [27]**.** Herbal medicines have recently attracted much attention as alternative medicines useful for treating or preventing life style related disorders of nephrotoxicity but relatively very little knowledge is available about their mode of action [28]. Triphala and its constituents *Terminalia chebula, Terminalia bellirica, Phyllanthus emblica* have shown much renal protective activity and significant protection against renal toxicity induced by insecticide Imidacloprid, which might be due to high levels of phenolic compounds. Triphala may be helpful in mitigating these particular side effects of such drugs generally. *Phyllanthus emblica revealed astonishing effect of renal protective responsibility comparing the four selected samples and confirmed practically.*

V. Conclusion

It is clear that the medicinal plants play a prominent role against various diseases. A variety of medicinal plants *Terminalia chebula, Terminalia bellirica, Phyllanthus emblica* and their extracts have been reported for its significant nephro protective activity is probably due to the presence of secondary metabolites present in the medicinal plants. Result of this study specified the fruits extracts of some medicinal plants have good potentials for use in kidney damage.

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