WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 19, 581-595. Research Article ISSN 2277–7105

IN-VIVO STUDIES ON NEPHROTOXICITY OF HABB-E-SURANJAN AN UNANI FORMULATION: A PRE-CLINICAL TRIAL

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Article Received on
12 August 2025,

Revised on 01 Sept. 2025,
Accepted on 21 Sept. 2025

https://doi.org/10.5281/zenodo.17221517

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ABSTRACT

Background: Unani medicine, an ancient system of healing, uses various herbal and mineral-based formulations to treat chronic inflammatory conditions. Habb-e-Suranjan is one such polyherbal Unani formulation primarily used for joint pain and gout. Unani philosopher Ibn Sina (980-1037 AD) stated that Suranjan is effective on niqras (gout) and waja-ul-mafasil (joint pain). Another renowned Unani philosopher, Daud Al-Antaki (1543-1599 AD), speculated that Suranjan is very effective for lower back pain, joint pain, and sciatica. The author of the book, Mo'tamad Fil Advia, Ibn Turkumani, mentioned that Suranjan has special positive and curative effects in the treatment of various forms of arthritis, niqras (gout), and numbness. He noted that it relieves pain immediately when applied in the form of zimad (ointment). These three statements support the idea that Habb-e-Suranjan possesses significant anti-inflammatory and analgesic effects. However, no data have been found regarding its nephrotoxicity with long-term use. For this reason, it is necessary to study the nephrotoxic effects of Habb-e-Suranjan. **Methodology:** This study investigates the nephrotoxicity of Habb-e-Suranjan in vivo using a controlled animal model, comparing its effects to Diclofenac Sodium, a widely used nonsteroidal anti-inflammatory drug (NSAID) known for its potential nephrotoxic side effects. The investigation was conducted in a dose-dependent manner using the Wistar Albino Rat model in a laboratory setting. A total of 25 rats were selected for the study and divided into five groups. An acute

oral nephrotoxicity test was carried out, which involved assessing kidney function through biochemical tests such as Serum Creatinine and Blood Urea Nitrogen (BUN), along with a histopathological examination of the kidneys. **Result:** The study observed the effects of Habb-e-Suranjan on kidney function and compared them with those of Diclofenac Sodium over different time periods. Biochemical parameters for kidney function tests were observed at weekly intervals. After 28 days, the control group and Habb-e-Suranjan-treated groups (17, 33, and 50 mg/kg body weight) consistently showed normal S. Creatinine and BUN levels, indicating that Habb-e-Suranjan didn't exhibit any nephrotoxic effect at the usual dose. However, the Diclofenac Sodium group (50 mg/kg body weight) demonstrated increased BUN and S. Creatinine levels, especially after 28 days, suggesting potential nephrotoxicity. The histopathological study indicated that Habb-e-Suranjan did not cause any nephrotoxic effects even at doses up to three times higher than the usual dose, while the Diclofenac Sodium (50 mg/kg body weight) group exhibited diffuse and significant nephrotoxic effects after 28 days of administration. **Conclusion:** Habb-e-Suranjan is safe for the kidneys at the usual dose, whereas Diclofenac Sodium exhibits nephrotoxic effects with long-term use. A large-scale trial is recommended to evaluate and confirm the toxicity of the drug.

KEYWORDS: Nephrotoxicity, Histopathological change, Habb-e-Suranjan, Tablet Diclofenac, Anti-inflammatory and Analgesic effects.

1. INTRODUCTION

Diclofenac sodium is one of the most popular and widely used painkillers for the management of musculoskeletal pain. Diclofenac-induced hepatotoxicity has been reported in various studies at the dose of 13.5 mg/kg b.w. (de Cássia Bergamaschi et al., 2006). Scientists have also studied hepatotoxic effects following oral administration of diclofenac at a dose of 9.5 mg/kg b.w. (Zhai et al., 2013). Test groups receiving diclofenac at a dose of 8mg/kg body weight showed toxic responses in the animal model (Tomic et al., 2008). *Tomic et al.* and other studies have reported both hepatotoxicity and renal toxicity of diclofenac (Tolman, 1998). The toxicity of diclofenac has been demonstrated in both animals and humans (Uyemura et al., 1997). The diclofenac derivatives involved in hepatotoxicity include 4′-hydroxy-3′-diclofenac, 5′-hydroxy-4-diclofenac, and 5′-hydroxy-6′-diclofenac (D'Abril Ruíz-Leyja et al., 2013). However, most toxicity studies of diclofenac have been conducted in vitro studies but not in in vivo studies (Gómez-Lechón et al., 2003; Khan & Ahmed, 2009).

Herbs are used therapeutically worldwide to treat various types of ailments. Polyherbal formulations represent the largest segment of the global herbal supplements and remedies market. In the Unani system of Medicine, compound formulations are prepared from herbal, mineral, and animal sources, with herbal ingredients comprising the majority. There are four basic dosage forms in Unani Medicine: solid, semisolid, liquid, and gaseous. These dosage forms are prepared from three origins collectively referred to as Mawaleed-e-Salasa (Three sources or origins of drugs). Habb or pill is a solid dosage form with several advantages. (Hamdani, 2011; Ahmad, 2015). Habb (pill) is an ancient dosage form of the Unani system of medicine invented by Hakeem Seelon (Husain, 2015). Habb is an Arabic word that means a pill, although it also refers to a seed. In the context of medicine, it refers to a round solid dosage form made from one or more ingredients derived from one, two, or all three origins. Habb-e-Suranjaan is a prominent compound formulation traditionally used for its analgesic and anti-inflammatory properties. There are more than ten types of Nuskhajat (formulations) of Habb-e-Suranjaan, which differ slightly in ingredients, weight, and binders. Despite these differences, all formulations are commonly used to treat waja-ul-mafasil (joint pain). The main ingredient in almost all versions is Suranjan Sheerin, with the exception of two versions, which will be discussed later. All the crude ingredients in Habb-e-Suranjan, including Suranjaan sheerin, have analgesic, anti-inflammatory, and purgative effects. Suranjaan sheerin is used in the treatment of arthralgia (Baitar, 1999; Razi, 2000), gout (Razi, 2000; Ghani, YNM), sciatica (Kabeeruddin, 2000; Sargodhwi, 2012), intestinal worm, jaundice, bone pain, sclerotitis, all types of arthralgia (Khan, 2014), and hemorrhoids. (Baitar, 1999; Khan, 2014). Beyond the pharmacological actions of its ingredients, Habb-e-Suranjaan as a compound formulation is indicated in arthralgia, sciatica (Kabeeruddin, 2010; Jilani, 2005; Majusi, 2010; Kabeeruddin, 1938), gout, paraplegia, Bell's palsy (Arzani, 2009), inflammation, pain, and restoration of sensation (Anonymous, 2006).

A review of the literature revealed that Habb-e-Suranjan has significant anti-inflammatory and analgesic properties. However, no data are available on its nephrotoxicity with long-term use. Therefore, it is necessary to investigate the potential nephrotoxicity of Habb-e-Suranjan. This formulation is primarily composed of Colchicum luteum (Suranjan), traditionally known for its anti-inflammatory and analgesic properties (CCRUM, 2007). However, like many polyherbal drugs, it requires rigorous pre-clinical safety evaluations to determine its toxicity profile, particularly renal toxicity, given the increasing reports of herb-induced nephrotoxicity (Ekor, 2014).

Non-steroidal anti-inflammatory drugs (NSAIDs) such as Diclofenac Sodium are commonly used for managing pain and inflammation but are associated with adverse renal effects, including interstitial nephritis and glomerular damage (Yap & Ismail, 2018). As a comparative standard, Diclofenac provides a relevant benchmark for evaluating the renal impact of alternative formulations like Habb-e-Suranjan.

This study aims to investigate the nephrotoxicity of Habb-e-Suranjan using an in vivo model, comparing its effect to Diclofenac Sodium to evaluate its safety for long-term use.

MATERIALS AND METHODS

This was a pre-clinical (Phase-0) study conducted in a laboratory setting using the Wistar Albino rat model. A total of 25 rats were selected and divided into five groups. An acute oral nephrotoxicity test was performed to assess kidney function through parameters such as serum creatinine, blood urea nitrogen (BUN), and histopathological examination of the kidneys. The toxicity study was carried out by daily oral administration of Tablet Diclofenac and Habb-e-Suranjan to different groups of rats over a period of 28 days. After the treatment period, the rats were sacrificed, and kidney function was assessed biochemically using standard techniques.

Experimental Design

Rats were divided into 5 groups.

Group 1: This group (n=5) will serve as the control. No medicine was used throughout the experiments, but they were given free access to normal food pellets and water ad libitum.

Group 2: This group (n=5) of rats administered Tablet Diclofenac orally (Toxic Dose, 50 mg/kg body weight) throughout the experiments but was given free access to normal food pellets and water ad libitum.

Group 3: This group (n=5) of rats administered Habb-e-Suranjan orally (Regular Dose, 17 mg/kg body weight) throughout the experiments but was given free access to normal food pellets and water ad libitum.

Group 4: This group (n=5) of rats administered Habb-e-Suranjan orally (Double Dose, 33 mg/kg body weight) throughout the experiments but was given free access to normal food pellets and water ad libitum.

Group 5: This group (n=5) of rats administered Habb-e-Suranjan orally (Suspected Dose, 50 mg/kg body weight mg/kg body weight) throughout the experiments but was given free access to normal food pellets and water ad libitum.

2 ~ 4 ml of blood from each Experimental rat in the tail will be drawn for the Biochemical assay every 7 and 14 days. After sacrificing the rat from the inferior vena cava for the Biochemical assay, 28 days of experiment. Histopathological examination of nephrotoxicity was assessed by biopsy.

Dose Calculation Formula

Animal Dose (mg/Kg) = Human Dose (mg/Kg) × Conversion factor [P. Janhavi, 2019]

Dose of Diclofenac

1) Human Dose (HD)= 150 mg/ Day

2) Human Equivalent Dose (HED) = $\frac{HD}{60\ Kg\ (Adult)} = \frac{150}{60}$ = 2.5 mg / Kg

3) Animal Equivalent Dose (AED) = HED× Conversion Factor = 2.5× 6.17 mg / Kg =15.43 mg / Kg

4) Average Animal Dose = $\frac{AED \times Animal\ Weight\ (gm)}{1000\ (gm)}$ mg / Wt. of Animal

= $\frac{15.43 \times 150\ gm}{1000}$ = 2.31 mg / 150 gm

Statistical Analysis

Microsoft Office Application (MS) Excel software to determine the significance of different biochemical test results and histopathology results.

RESULTS

Result: Table 1: The renal profile parameters among 5 groups of Wistar Albino rats after the specified dosage administration (n=15). On the date of 20/08/23 (7th day).

Renal Profile Parameter	Group-I (n=3) Control No Medicine	Group-II (n=3) Diclofenac 50 mg/kg	Group-III (n=3) Habb-e-Suranjan Regular 17 mg/kg	Group-IV (n=3) Habb-e-Suranjan Double 33 mg/kg	Group-V (n=3) Habb-e-Suranjan Suspected 50mg/kg	Normal Range
Creatinine (mg/dL)	0.6, ± 0.1	0.8, ± 0.1	0.6, ± 0.1	0.7, ± 0.1	0.8, ± 0.1	0.7-1.2
BUN (mg/dL)	27, ± 2	40, ± 3	27, ± 2	30, ± 1	36, ± 2	7-40

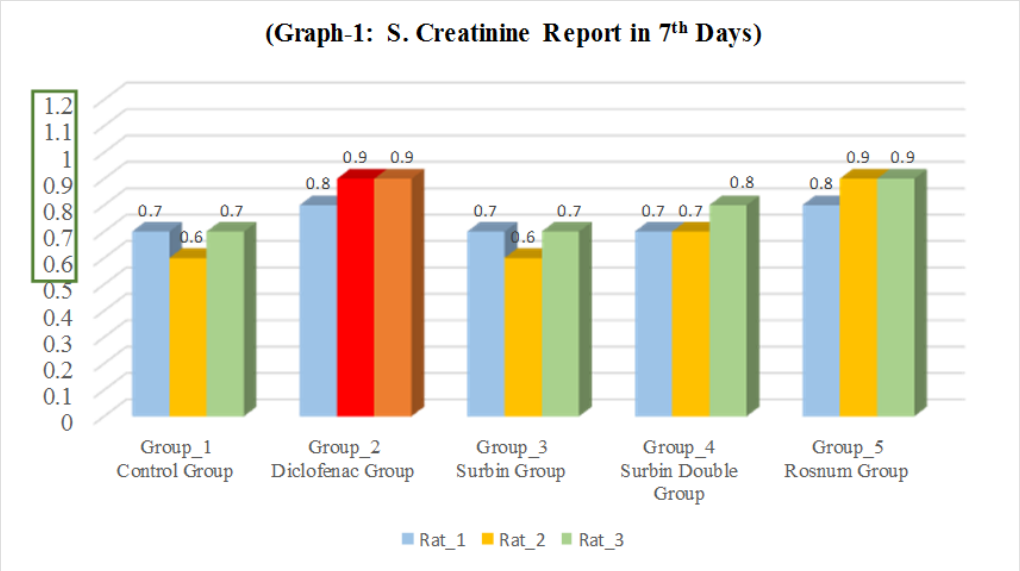


Table 5.2: The renal profile parameters among 5 groups of Wistar Albino rats after the specified dosage administration (n=15). On the date of 27/08/23 (14th day).

Renal Profile Parameter	Group-I (n=3) Control No Medicine	Group-II (n=3) Diclofenac 50 mg/kg	Group-III (n=3) Surobin Regular 17 mg/kg	Group-IV (n=3) Surobin Double 33 mg/kg	Group-V (n=3) Surobin Suspected 50mg/kg	Normal Range
Creatinine (mg/dL)	0.6, ± 0.1	1.0, ± 0.1	0.7, ± 0.1	0.7, ± 0.1	0.8, ± 0.1	0.7-1.2
BUN (mg/dL)	29, ± 3	41, ± 3	28, ± 2	31, ± 2	32, ± 2	7-40

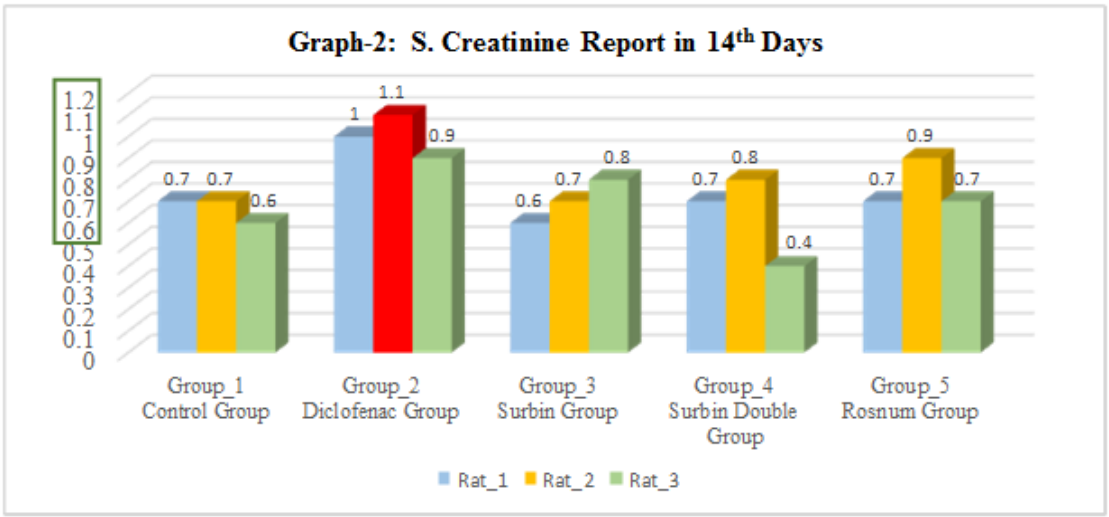
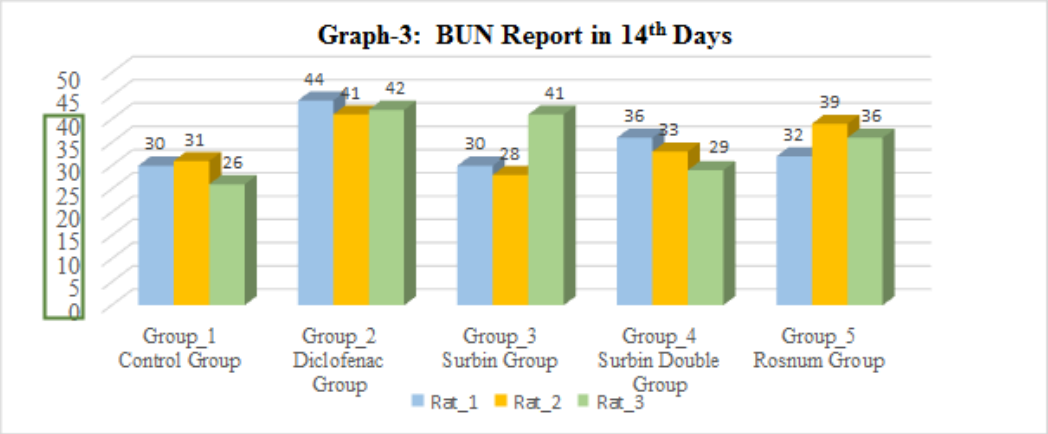
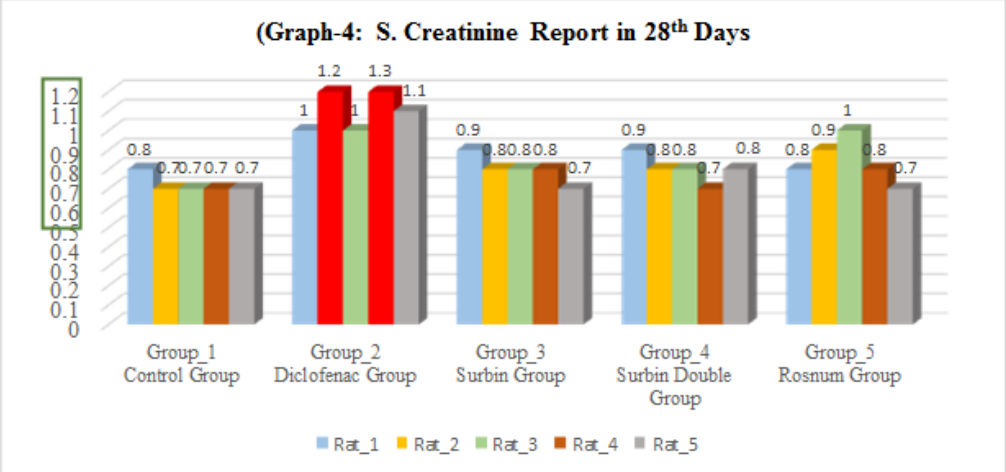


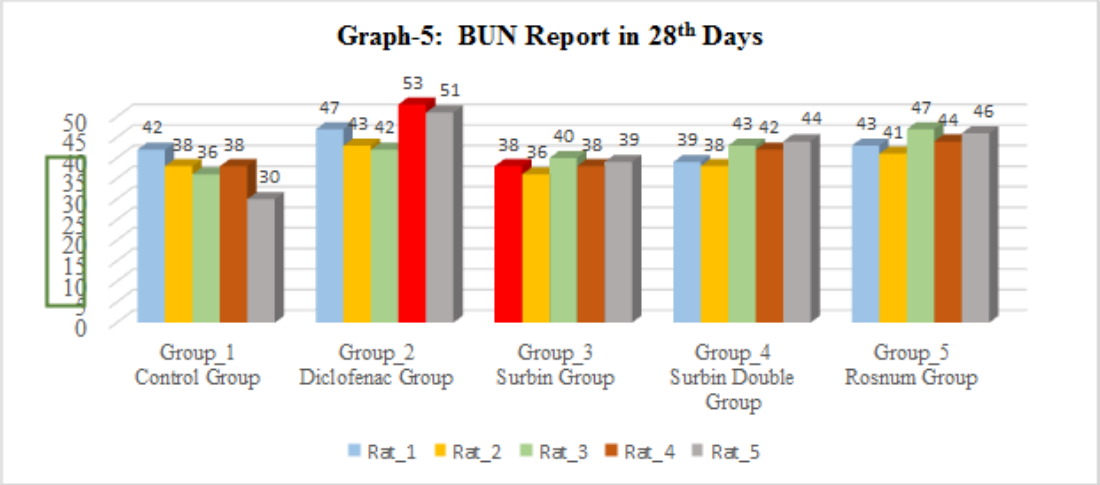
Table 3: The renal profile parameters among 5 groups of Wistar Albino rats after the specified dosage administration (n=25). On the date of 10/09/23 (28th day):

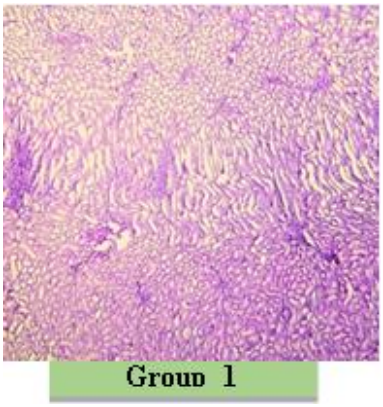
Renal Profile Parameter	Group-I (n=5) Control No Medicine	Group-II (n=5) Diclofenac 50 mg/kg	Group-III (n=5) Surobin Regular 17 mg/kg	Group-IV (n=5) Surobin Double33 mg/kg	Group-V (n=5) Surobin Suspected 50mg/kg	Normal Range
Creatinine (mg/dL)	0.7, ± 0.1	1.2, ±0.1	0.8, ± 0.1	0.9, ± 0.1	1.0, ± 0.1	0.7-1.2
BUN (mg/dL)	36, ± 2	48, ± 5	38, ± 2	42, ± 3	44, ± 3	7-40



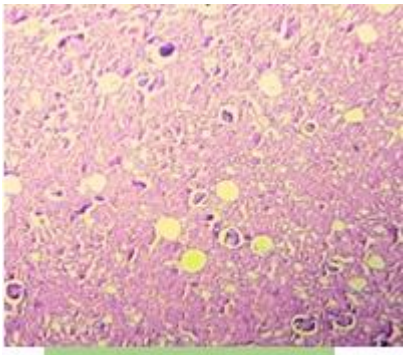


Histopathology study image: The renal histopathological parameters among 5 groups of Wistar Albino rats after the specified dosage administration (n=5). On the date of 10/09/23 (28th day)





Group 1



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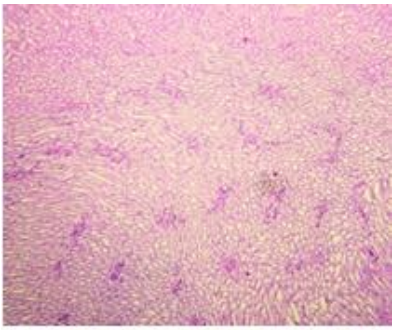
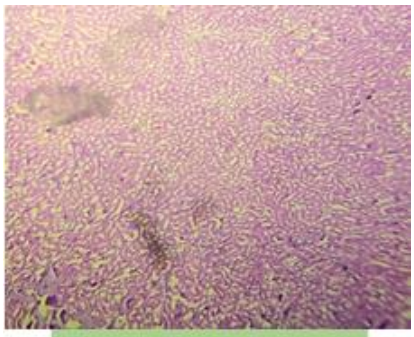
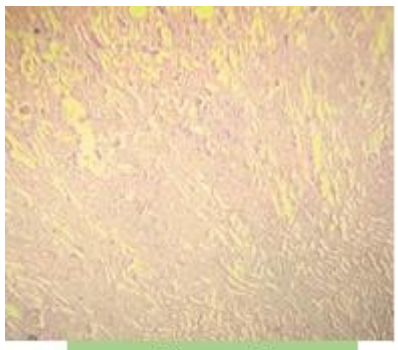


Group_3



Group_4



Group_5

The data in Table 1 show that serum creatinine and blood urea nitrogen (BUN) levels remained within normal limits for the control group and all groups treated with Habb-e-Suranjan at varying doses (17, 33, and 50 mg/kg body weight). In contrast, the group treated with Diclofenac Sodium (50 mg/kg body weight) exhibited elevated BUN levels (40 ± 3 mg/dL), indicating potential nephrotoxicity. After 7 days of administration, only the Diclofenac group showed a significant increase in BUN compared to the control and Habb-e-Suranjan groups.

Table 2 (14th Day): Serum Creatinine (S. Creatinine) and Blood Urea Nitrogen (BUN) levels were measured across five groups. The control group and the Habb-e-Suranjan-treated groups (at doses of 17, 33, and 50 mg/kg b/w) maintained normal levels of both markers. However, the Diclofenac Sodium group (50 mg/kg b/w) showed elevated BUN (41 ± 3 mg/dL) and S. Creatinine (1.0 ± 0.1 mg/dL), indicating possible renal stress or damage.

Table 3 (28th Day): A more pronounced increase in S. Creatinine and BUN was observed in the Diclofenac Sodium group (S. Creatinine: 1.2 ± 0.1 mg/dL, BUN: 48 ± 5 mg/dL), confirming nephrotoxicity with prolonged use. In comparison, Habb-e-Suranjan groups showed moderate increases in both parameters, but values remained closer to the control group.

The data across Tables 1 to 3 indicate a time-dependent effect of treatments on kidney function. Over 7, 14, and 28 days, serum creatinine and BUN levels remained within normal limits for the control and Habb-e-Suranjan groups at all tested doses. In contrast, the Diclofenac Sodium group (50 mg/kg b/w) showed a progressive and significant increase in both markers, particularly BUN, indicating nephrotoxicity. These findings suggest that Habb-e-Suranjan is safer for renal function compared to Diclofenac Sodium with prolonged use.

DISCUSSION

The present study investigated the nephrotoxic potential of Habb-e-Suranjan, a traditional Unani formulation, in comparison to Diclofenac Sodium, a well-known non-steroidal anti-inflammatory drug (NSAID) with reported nephrotoxic effects. Using the Wistar albino rat model, the study evaluated serum creatinine, blood urea nitrogen (BUN), and histopathological changes in the kidneys over a 28-day period.

Biochemical findings demonstrated that serum creatinine and BUN levels in the control group and all Habb-e-Suranjan-treated groups (17, 33, and 50 mg/kg body weight) remained within normal physiological limits throughout the observation period. In contrast, the Diclofenac Sodium group (50 mg/kg b.w.) showed a consistent and progressive elevation in both serum creatinine and BUN levels. After 7 days, the BUN level in the Diclofenac group rose significantly to 40 ± 3 mg/dL compared to the control (27 ± 2 mg/dL), suggesting early signs of renal stress.

On the 14th day, this nephrotoxic trend persisted, with the Diclofenac group exhibiting serum creatinine and BUN levels of 1.0 ± 0.1 mg/dL and 41 ± 3 mg/dL, respectively, which were significantly higher than those of the Habb-e-Suranjan-treated groups. By day 28, the nephrotoxicity in the Diclofenac group was further confirmed, with serum creatinine rising to 1.2 ± 0.1 mg/dL and BUN to 48 ± 5 mg/dL, indicating cumulative renal impairment. These findings are in line with earlier studies that have reported Diclofenac-induced renal toxicity through mechanisms involving oxidative stress, mitochondrial dysfunction, and inhibition of renal prostaglandin synthesis (Bort et al., 1999; Whelton, 1999; Nasr, 2013).

Conversely, Habb-e-Suranjan exhibited a relatively nephroprotective profile. Across all doses tested, the formulation did not significantly elevate serum creatinine or BUN compared to the control group. Even at the highest dose (50 mg/kg), the values remained within acceptable limits (S. Creatinine: 1.0 ± 0.1 mg/dL; BUN: 44 ± 3 mg/dL), suggesting that while minor renal stress might occur at higher doses, the effect is substantially lower than that caused by Diclofenac.

Histopathological analysis further supported the biochemical data. The kidneys of rats in the control and low-dose Habb-e-Suranjan groups (17 mg/kg) appeared histologically normal. Mild necrosis was observed in the 33 mg/kg Habb-e-Suranjan group, and limited necrosis confined to mononuclear cells was seen at the 50 mg/kg dose, indicating a dose-dependent but relatively mild renal effect. In contrast, the Diclofenac Sodium group exhibited extensive necrosis and inflammatory infiltration, consistent with NSAID-induced nephrotoxicity (Murray & Brater, 1993).

These findings suggest that Habb-e-Suranjan, despite being a traditional formulation, possesses a safer renal profile in comparison to Diclofenac. Previous studies on herbal and Unani preparations such as Colchicum autumnale, the primary ingredient in Habb-e-

Suranjan, have also suggested potential anti-inflammatory benefits with fewer renal side effects (Amin et al., 2005). However, its nephrotoxicity at higher doses or with prolonged use requires further investigation.

Recommendations

It is recommended to use Habb-e-Suranjan for humans by maintaining a proper dose; there is a need for proper guidelines for pharmaceutical companies about Habb-e-Suranjan.

CONCLUSION

Habb-e-Suranjan demonstrated a comparatively safe nephrotoxic profile in the Wistar rat model. While Diclofenac Sodium significantly affected renal function and structure, Habb-e-Suranjan maintained kidney integrity and function across a 28-day administration period. These results support the traditional use of Habb-e-Suranjan as a safer alternative in conditions requiring anti-inflammatory therapy, though caution is advised at higher doses. Further studies are recommended to explore its mechanism of action, long-term safety, and potential clinical application.

ACKNOWLEDGEMENT

The authors sincerely acknowledge the Faculty of Unani and Ayurvedic Medicine, Hamdard University Bangladesh, and the Department of Pharmacy, Jahangirnagar University, for their constant guidance and valuable support.

Conflicts of interest

No conflicting interests are stated by the authors

Limitation

Due to technical, logistical, and financial constraints, we did not conduct the study on a large scale.

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