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Review article

Therapeutic Input of Melatonin on Nephrotoxicity

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ABSTRACT:

Objectives: The health impact of melatonin cannot be overemphasized. The therapeutic input of melatonin on nephrotoxicity was explained.

Experimental approach: Search engines like Pubmed, Google Scholar and Crossref were used to review various literatures. The review done April 2022 – July 2022 considered literatures that reported the therapeutic input of melatonin on nephrotoxicity. The therapeutic input of melatonin on nephrotoxicity was searched using the following search keys "Melatonin therapeutic input", Melatonin and nephrotoxicity,".

Findings and discussion: The therapeutic input of melatonin on nephrotoxicity was confirmed with 35 reports which were found suitable. These reports showed that nephrotoxicity caused by various chemicals and drugs can be alleviated with melatonin which is an endogenous hormone of sleep induction.

Conclusion: Melatonin showed ameliorative impact on nephrotoxicity induced by different chemicals and drugs, forming basis for inclusion of melatonin as therapeutics for nephrotoxicity.

Keywords: Melatonin, nephrotoxicity, therapeutic, chemicals, drugs.

1. INTRODUCTION

The maintenance of constant internal environment (homeostasis) is important in creating a state of balance among all the body systems needed for the body to survive and function correctly [1]. Homeostasis is responsible for regulation of temperature, maintaining healthy blood pressure, maintaining calcium levels, regulating water levels, defending against viruses and bacteria [2]. A number of organs are involved in this maintenance (homeostasis) and these include the kidney, lungs, pancreas and skin [3].

The kidneys are organs that their major role is maintaining homeostasis by managing fluid levels [4], electrolyte balance [5], waste excretion [6], reabsorption of nutrients [7], maintaining P^H [8], osmolality regulation [9], regulation of blood pressure [10], secretion of active compounds like erythropoietin a hormone which controls erythropoiesis [11], rennin an enzyme that helps manage the expansion of arteries and the volumes of blood plasma, lymph and interstitial fluid [12]and calcitriol a hormonally active metabolite of vitamin D that reabsorbs phosphate and increasing the amount of calcium that the intestines can absorb [13].

Diseases or dysfunction leading to nephrotoxicity or renal toxicity are often caused by drugs like acetaminophen [14], vancomycin [15], antiretrovirals [16], indinavir [17], chemicals, industrial or environmental toxic agents like mercury [18], arsenic lead [19], trichloroethylene [20], bromate[21], brominated-flame retardants [22], diglycolic acid [23], ethylene glycol [24], cadmium [25], acrylamide [26]

Drugs and plants have been shown to alleviate nephrotoxicity [27]. Melatonin has been proven to be beneficial in the treatment of nephrotoxicity [28]. Melatonin is a hormone produced in response to darkness and reduces with light [29]. It regulates the 24-hour circadian rhythm (night and day cycles) [30]. It has been shown to be used in depression, chronic pain, dementia and several sleep disorders like syncope [31]. In this study, the therapeutic input and effect of melatonin on nephrotoxicity was considered. This will form basis for the introduction of the use of melatonin in the cure and management of nephrotoxicity.

2. METHODOLOGY

Literature review was carried out for the period of three months (April 2022-July 2022) on different research search database such as PubMed, Google scholar, Crossref metadata. Therapeutic input of melatonin on nephrotoxicity was searched using the following search keys; "Melatonin therapeutic input""Melatonin and nephrotoxicity" "**T**herapeutic input of melatonin on nephrotoxicity". The results obtained are summarized below (Table 1).

3. FINDINGS

Thirty-five (35) reports were selected for therapeutic input of melatonin on nephrotoxicity**;** suggesting its essential

therapeutic input on nephrotoxicity induced by certain drugs and harmful substances (Table 1).

Table 1: Summary of findings on melatonin input on nephrotoxicity induced by different substances

S/No.	Input of melatonin on nephrotoxicity	Study support
1	Melatonin prevents aluminium induced nephrotoxicity by enhancing the antioxidant defense system	[32]
2	Melatonin confers protection against the oxidative damage associated with cisplatin-induced nephrotoxicity	[33,38,39,58]
3	Melatonin prevents nephrotoxicity induced by gentamicin in rats by restoring antioxidant enzyme activity	[34, 35,37,45]
4	Protective effect of melatonin against colistin-induced nephrotoxicity	[36]
5	Concomitant use of melatonin and vitamin E could be effective on prevention of acetamiprid-induced nephrotoxicity	[40]
6	Melatonin protects against the oxidative damage associated with acetaminophen induced nephrotoxicity	[41]
7	Melatonin and S-methylisothiourea has anti-inflammatory properties and antioxidants properties on mechlorethamin induced nephrotoxicity	[42]
8	Melatonin protects against amikacin-induced acute renal injury in rats	[43}
9	Melatonin through its antioxidant properties provides protection against cyclosporine-induced nephrotoxicity.	[44,50,54]
10	Melatonin offers some benefit as a potential agent to treat acute uranium induced nephrotoxicity	[46]
11	Combined protective effects of curcumin and melatonin on cisplatin-induced nephrotoxicity in rats	[47]
12	Melatonin ameliorates cyclophosphamide-induced nephrotoxicity	[48]
13	Combined protective effects of captopril, olmesartan, melatonin and compound 21 on doxorubicin-induced nephrotoxicity	[49]
14	Protective effect of melatonin on daunorubicin and doxorubicin induced nephrotoxicity.	[51,55]
15	Combined protective effects of lycopene and melatonin on methotrexate-induced nephrotoxicity	[52]
16	Melatonin is used for the prevention of ciprofloxacin-induced nephrotoxicity	[53]
17	Melatonin and mycophenolatemofetil together or separately protect against nephrotoxicity induced by tacrolimus	[56]
18	Melatonin protects against tenofovir-induced nephrotoxicity	[57,65]
19	Protective effect of melatonin and agomelatine on Adriamycin-induced nephrotoxicity	[59]
20	Melatonin could be used for reducing chronic cyclosporin A induced nephrotoxicity	[60]
21	Melatonin ameliorates fluoride-induced nephrotoxicity	[61]
22	Melatonin and insulin protects against streptozotocin induced nephrotoxicity	[62]
23	Melatonin ameliorates carbon tetrachloride-induced kidney injury	[63]
24	Melatonin and hesperid in ameliorates acetaminophen-induced nephrotoxicity	[64]
25	Melatonin protects against radiation induced nephrotoxicity	[66]

4. DISCUSSION

Melatonin is a hormone produced in the pineal gland located in the brain [67]. It is produced in response to darkness hence its name hormone of darkness [68]. The production is blocked when exposed to light [69]. It is also in exogenous forms [70].

Melatonin has been reported to play important roles in the body like sleep, sleep disorders antioxidant, immune system, cancer, reproduction, mood, aging [71].

This study provided the therapeutic input of melatonin on nephrotoxicity. Nephrotoxicity is a condition of fast decline in kidney function as a result of poisonous effects of medications like (acetaminophen, ciprofloxacin, ampicillin etc.) and chemicals like mercury, lead, cadmium, ethylene glycol, glycolic acid, arsenic, trichloroethylene, acrylamide etc. [14-26].

This study found out that melatonin has therapeutic input on various causes of nephrotoxicity like aluminium,cisplatin, gentamicin, colistin, acemiprid, acetaminophen, mechlorethamin, amikacin, cyclosporine, uranium, cyclophosphamide, doxorubicin, methotrexate, ciprofloxacin, tacrolimus, tenofovir, adriamycin, cyclosporine, fluoride, streptozotocin, carbon tetrachloride, radiation; which is as a result of its antioxidant, anti-inflammatory, immune boosting activities etc.[Table 1].

Nephrotoxicity caused by several chemicals and drugs (Table 1) through induction of oxidative stress, increase in the levels of lipid peroxidation and nitric oxide, decrease in levels of glutathione, various antioxidant enzymes, Nrf2 & mRNA expression, inflammation, nitrosative stress, apoptosis, acute and chronic renal injuries, increased serum blood urea nitrogen &creatinine levels, increased BCl_2 associated X protein, malondialdehyde, IL-6, IL-1β and TNF-α levels [32-65]. Oxidative stress/ damage are as a result of an imbalance between free radical activity and antioxidant activity. These free radicals could be harmful or beneficial. Oxidative stress could lead to a lot of conditions which include diabetes, cancer, heart disease, nephrotoxicity etc. but could be prevented by increasing the levels of antioxidants through diet and decreasing the formation of free radicals [32-36]. In this study, melatonin alleviates nephrotoxicity through its antioxidant properties as Table 1 showed that oxidative stress induced by aluminum [32], cisplatin [33], gentamicin [34], colistin [36],acetamiprid [40], acetaminophen [41], mechlorethamin [42],cyclosporine [44], uranium [46], cyclophosphamide [48], ciprofloxacin [53], tacrolimus [56], tenofovir [57], chronic cyclosporine A [60], carbon tetrachloride [63] was ameliorated by melatonin through enhancing antioxidants (Table 1). Melatonin

decreased blood urea nitrogen, creatinine lipid peroxidation and nitric oxide levels and increased the levels of gluthatione indicating attenuation in renal injury [32-34,40-43,48,53,56,61-64].

Melatonin also increased the activities of the antioxidant enzymes GPx (gluthatione peroxidase), SOD (superoxide dismutase), CAT(catalase) and GR (gluthatione reductase) and also suppressed the apoptotic effect by enhancing Bcl-2 protein expression in the kidney and decreasing the expression levels of proinflammatory cytokines, IL-6, IL-β and TNF-α levels, malondialdehyde which led to improvements in renal functions, oxidative stress parameters, inflammatory markers [Table 1].

5. CONCLUSION

Therapeutic input of melatonin on nephrotoxicity suggests that melatonin could be used to alleviate the fast rising kidney issues associated with various substances, forming basis for incorporating melatonin as therapeutics for nephrotoxicity.

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