

ORIGINAL ARTICLE



## Effects of *Achillea millefolium* on cisplatin induced ocular toxicity: an experimental study

Ufuk Okay<sup>a</sup>, Irmak Ferah Okay<sup>b</sup>, Ismail Cagri Aydin<sup>a,c</sup>, Cemil Bayram<sup>a</sup>, Muhammed Sait Ertugrul<sup>d</sup>, Arzu Gezer<sup>e</sup> and Ahmet Hacimuftuoglu<sup>a</sup>

<sup>a</sup>Department of Medical Pharmacology, Faculty of Medicine, Ataturk University, Erzurum, Turkey; <sup>b</sup>Department of Pharmacology, Faculty of Pharmacy, Ataturk University, Erzurum, Turkey; <sup>c</sup>Department of Pharmacology, Faculty of Pharmacy, Erzincan Binali Yildirim University, Erzincan, Turkey; <sup>d</sup>Department of Pharmacology, Faculty of Pharmacy, Agri Ibrahim Cecen University, Agri, Turkey; <sup>e</sup>Department of Histology, Vocational School of Health Services, Ataturk University, Erzurum, Turkey

### ABSTRACT

**Aim:** Cisplatin is a widely used and highly effective anti-cancer agent and one of the limiting side effects of cisplatin is ocular toxicity. *Achillea millefolium*, also known as yarrow, is a plant that has been used for many years to treat various health problems including chemotherapy-related toxicities.

**Methods:** The present investigation was designed to evaluate the biochemical, molecular and histopathological effects of *Achillea Millefolium* on cisplatin-induced oxidative and inflammatory ocular damage in rats. Twenty-four adult male rats were assigned randomly to four groups ( $n = 6$ ) as (1) control, (2) cisplatin (7 mg/kg, intraperitoneally), (3) Cisplatin + *Achillea millefolium* (200 mg/kg, orally for 14 consecutive days), (4) Cisplatin + *Achillea millefolium* (400 mg/kg, orally for 14 consecutive days). Levels of total antioxidant capacity and total oxidant status, SOD, MDA, IL-1 $\beta$ , and IL-10 were measured in ocular tissue. The mRNA expressions of TNF- $\alpha$ , nuclear factor kappa B and Caspase-3 were evaluated. Also, ocular sections were evaluated histopathologically.

**Results:** *Achillea Millefolium* upregulated ocular antioxidant enzymes and downregulated inflammation. The SOD activity and total antioxidant capacity increased whereas total oxidant status and MDA levels decreased significantly at high dose group. High dose *Achillea millefolium* treatment reduced the IL-1 $\beta$  concentrations, whereas IL-10 levels increased significantly in that group. Moreover, we observed that *Achillea millefolium* restored ocular histopathological structure and significantly suppressed apoptosis by reducing the expression of Caspase-3.

**Conclusion:** Collectively, our results suggest that *Achillea millefolium* have protective effects against cisplatin-induced ocular toxicity and is a promising adjuvant therapy with the potential to prevent cisplatin related ocular toxicity.

### ARTICLE HISTORY

Received 26 January 2021

Revised 24 March 2021

Accepted 10 April 2021

### KEYWORDS

*Achillea millefolium*;  
cisplatin; ocular toxicity; rat;  
oxidative stress;  
inflammation; apoptosis

## 1. Introduction

Cisplatin (CP) is a platinum based anticancer drug that forms platinum complexes upon binding to DNA and causes conformational changes resulting in apoptosis by interfering with transcription and replication<sup>1</sup>. CP has shown anticancer activity in a variety of cancers including squamous cell carcinoma, head, neck, testicular, ovarian, bladder and prostate cancers, cervical tumours, and non-small cell lung carcinoma<sup>2</sup>. CP has been linked to various toxic side effects on eye, gastrointestinal, nervous, renal and reproductive systems which limit its clinical effectiveness<sup>3,4</sup>. Reported ocular side effects of CP include retinal toxicity, bleeding, visual impairment, pigment changes, cone dysfunction, blindness, and retinal ischaemia<sup>5</sup>. It has been reported that the ocular side effects of CP is associated with its accumulation in the central nervous system<sup>6</sup>. Moreover, CP reduces antioxidant enzyme activities, increase reactive oxygen species and lipid peroxidation, which cause tissue damage through various reactions,

and thus leads to cell damage and death<sup>7</sup>. Proinflammatory cytokines have also been reported to play a key role in the pathogenesis of CP induced retinal and optic nerve injury.

In the light of all these data, it is obvious that oxidative stress and inflammation have a potential role in the aetiology of CP associated ocular toxicity<sup>8</sup>. Recent investigations have also proved this information and implied that antioxidant and anti-inflammatory agents might attenuate the side effects of CP<sup>9,10</sup>.

*Achillea millefolium* L (AM), also known as yarrow, is a plant that has been used for many years to treat various health problems<sup>11</sup>. This herb is widely used for the treatment of spasmodic gastrointestinal disorders, hepatobiliary, gynecological disorders and wound healing<sup>12</sup>. In recent years AM has also been reported to have other effects, including antioxidant<sup>13</sup>, anti-inflammatory<sup>14</sup>, antibacterial<sup>15</sup>, anti-hepatotoxic<sup>11</sup> and anticancer<sup>16</sup> activities. A significant part of AM's effects comes from its high amounts of polyphenolic compounds<sup>17</sup>. It has also been reported that especially its