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Free Radical Scavenging and Antinociceptive Activities of the Aqueous Extract from *Matricaria chamomilla* L. Flowers

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ABSTRACT

Background: *Matricaria chamomilla* L. is a famous medicinal plant distributed worldwide. It is widely used in traditional medicine to treat all kinds of diseases, including infections, neuropsychiatric, respiratory, gastrointestinal, and liver disorders. It is also used as a sedative, antispasmodic, antiseptic, and antiemetic. Our aims in this study was thus to quantify the phenolic, flavonoids contents in the flower of this plant, and also to evaluate the *in vitro* antioxidant potential and the *in vivo* analgesic activity. Methods: The total phenolic and flavonoid contents of the plant aqueous extract (MCAqE) were estimated using the Folin–Ciocalteu and $AlCl_3$ colorimetric methods, respectively. However, DPPH method was used to evaluate the *in vitro* antioxidant activity. Analgesic activity was tested by acetic acid induced writhing model in mice. Results: Quantitative determination of total polyphenols and flavonoids revealed that this extract contained 158.41±1.6 mg gallic acid equivalent/g of dry extract and 37.06±0.56 mg quercetin equivalent/g of dry extract, respectively. The antioxidant activity of the plant extract was important (IC_{50}=3.08±0.25 mg/mL). MCAqE extract, at 400 mg/kg, showed analgesic activity (39.60±8.70%) against acetic acid induced pain in mice while the standard reference drug Diclofenac sodium exhibited 90.44±2.80% activity at 10 mg/kg dose.

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Introduction

Reactive oxygen species (ROS) is a collective term that broadly describes O_2-derived free radicals such as superoxide anions ($O_2^{\bullet-}$), hydroxyl radicals (HO•), peroxyl (RO_2•), alkoxyl (RO•), as well as O_2-derived non-radical species such as hydrogen peroxide (H_2O_2) (Circu and Aw, 2010; Sevindik et al., 2017; Mohammed et al., 2022).

In vivo, some of these ROS play a positive role such as energy production, phagocytosis, regulation of cell growth and intracellular signaling (Loucif et al., 2020 a). But if they reach high levels, oxidative stress in human body would be created, which leads to a variety of biochemical and physiological lesions and often results in metabolic impairment and cell death (Mehlous et al., 2020; Pehlivan et al., 2021). So, the term "oxidative stress" implies that the physiological balance between the creation of ROS and the ability to detoxify these molecules has been upset, leading to resultant stress and damage to cellular systems. Importantly, this can either indicate that there may be an abnormal elevation in ROS generation, or that there may be deficiencies in antioxidant defense systems (Kaoudoune et al., 2020; Kına et al., 2021; Uysal et al., 2021).

Antioxidants are substances that either directly or indirectly protect cells against adverse effects of xenobiotics, drugs, carcinogens and toxic radical reactions (Mate, 2000; Akgül et al., 2022). Many medicinal plants include large amounts of antioxidants such as phenolic compounds, nitrogen compounds, vitamins, terpenoids and other endogenous metabolites (Ozkan et al., 2016; Unal et al., 2022).

M. chamomilla a member of the Asteraceae family, has been used by humans for centuries. It occurs naturally practically all over the world including Europe, Asia and Northern Africa, and it is also cultivated in Northern America (Haghi et al., 2014; Viapian et al., 2016). *M. chamomilla* is often used as a medicinal plant, due to its anti-inflammatory, analgesic, sedative, antimicrobial, anti-allergic, anti-hyperglycemia and anti-spasmodic effects (Haghi et al., 2014). *M. chamomilla* is rich in flavonoids, which are effective antioxidants in neutralizing free radicals (Sayyar et al., 2018).

Interest in natural antioxidants, especially those found in plants, has increased in recent years (Krupodorova et al., 2022). Phenols, flavonoids, and various herbal extracts have been reported as antioxidants, and these natural antioxidants display a wide range of biological effects, including analgesic activity.

M. chamomilla is a medicinal plant widely used in Algeria. So our aims in this study were thus to quantify the phenolic and flavonoids contents in the flower of this plant, and to evaluate the *in vitro* antioxidant and the analgesic activity *in vitro*.

Materials and Methods

Plant Material

M. chamomilla flowers were gathered by Pr. Amira smain from the region Serif North-Eastern part of Algeria in February and dried in a shaded and ventilated place for many days at the laboratory.

Preparation of the Aqueous Extracts

Dried and powdered chamomile flowers were extracted by the method of Loucif et al., (2020b). 25 g of powder was boiled in 1 liter of distilled water for 30 minutes. The mixture was filtered through Wattman filter paper and dried at 45°C to obtain an aqueous extract.

Determination of Total Polyphenols Content

Total phenolic content was estimated using the Folin–Ciocalteu colorimetric method as described by Mehlous et al. (2020 a). A volume of 100 µL of MCAqE extract was mixed with 500 µL of Folin-Ciocalteu reagent (diluted 10 times). After 4 min, 400 µL of 7.5% sodium carbonate (Na_2CO_3) solution was added. The final mixture was shaken and then incubated for 90 min in dark at room temperature. Results were expressed as mg of gallic acid equivalent (GAE) per g of dry material.

Determination of Total Flavonoids Content

Total flavonoid content was determined by the $AlCl_3$ colorimetric method as described by Benabdallah et al. (2020). A volume of 500 µL of the sample was mixed with 500 µL of 2% aluminium chloride solution. After incubation for 10 min at room temperature, the optical density of the reaction mixture was evaluated at 430 nm. Quercetin was used as a citation standard and the total flavonoid content was expressed as mg of quercetin equivalent per gram of dry weight (mg QE/g DW).

Determination of Antioxidant Capacity

Determination of antioxidant capacity of MCAqE was performed by a simple assay using the stable DPPH radical with the method described by Mamache et al. (2022), where a volume of 50 µL of different dilutions of the plant extract was added to 1250 µL of DPPH solution (0.004%). After 30 min of incubation at room temperature, the absorbance was measured at 517 nm. Gallic acid was used as standard. Scavenging activity (SA) of the plant sample was determined by the following equation:

$$SA\ (\%) = \left(\frac{\text{Control absorbance} - \text{Sample absorbance}}{\text{Control absorbance}}\right) \times 100$$

Antinociceptive Activity

Female Albino Wistar mice (180-220 g) were used for assessing the antinociceptive activity. The animals were maintained under standard laboratory conditions and had free access to food and water ad libitum. The animals were divided into 4 groups, each consisting of six animals which were fasted overnight prior to the experiments. The animals were obtained from Pasteur Institute (Algeria).

Acetic Acid-induced Writhing Test

The antinociceptive activity of the samples was also studied using acetic acid- induced writhing model in mice (Aoki et al., 2006). The animals were divided into four groups with six mice in each group. Group I animals received distilled water, group II received Diclofenac sodium at 10 mg/kg body weight, while animals of groups-III and IV were treated with 200 mg/kg and 400 mg/kg body weight, of the aqueous extract of *M. chamomilla* flowers by gavage. Test samples, distilled water and Diclofenac sodium were administered orally 60 min before intraperitoneal administration of 1 % (v/v) acetic acid. After an interval of 5 min, the mice were observed for specific abdominal contraction referred to as 'writhing' for the next 20 minutes.

The Analgesic activity was expressed as a percentage of inhibition (I) of abdominal writhes.

$$I(\%) = \frac{(NWC - NWT)}{NWC}$$

NWC: Number of writhes (control)
NWT: Number of writhes (test)

Statistical Analysis

Statistical analyses and graphs were done using GraphPad Prism 7.0 software. The data were expressed as mean ± standard deviation (SD) and the significance of difference was calculated using one-way ANOVA and Student test. Values of $p<05$ were considered significant.

Results

Total Phenolic and Flavonoid Contents

The total phenolic and total flavonoid contents were calculated on the basis of gallic acid and quercetin and expressed as equivalents of mg gallic acid and quercetin per g of dry material, respectively. The amounts of total phenolics and flavonoid are shown in Table 1. The plant extract was rich in phenolics acid (158.41±1.6 mg GAE/g DW) and flavonoids content was found to be 37.06±0.56 mg QE/g DW

Table 1. Total phenolic and flavonoids contents of *M. chamomilla* L. aqueous extract

	MCAqE
Total phenolic content (mg gallic acid/g of dry material)	158.41±1.6
Total flavonoids content (mg quercetin /g of dry material)	37.06±0.56

Table 2. Antioxidant activity of MCAQE

Extract	IC_{50} mg/mL
MCAQE	3.08±0.25****
Gallic acid	0.033±0.0005

Data were presented as IC_{50} means ± SD (n=3. **** P<0. 0001 *vs* gallic acid as standard.

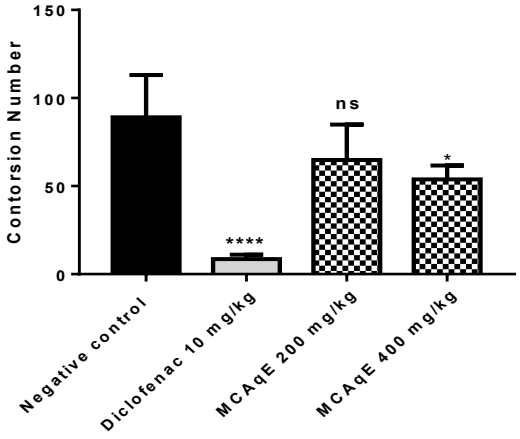

Figure 1. Effects of MCAqE extract (200 and 400 mg/kg) and Diclofenac (10 mg/kg *p.o*.) on intraperitoneal acetic acid-induced writhing in mice. Each column represents the mean±SEM (n=5). Asterisks indicate significant difference from control. *P< 0.01, ****P<0.0001, ns: not significant *vs* negative control.

Antioxidant Activity

DPPH test, which is based on the ability of DPPH, a stable free radical, to decolorize in the presence of antioxidants, is a direct and reliable method for determining radical scavenging action. The DPPH radical contains an odd electron, which is responsible for the absorbance at 515-517 nm and also for a visible deep purple color. When DPPH accepts an electron donated by an antioxidant compound, the DPPH is decolorized, which can be quantitatively measured from the changes in absorbance (Hasan et al., 2009). IC_{50} value describes how plant extract has antioxidant activity, where a lower IC_{50} points to the higher antioxidant activity. Gallic acid was chosen as the reference antioxidant for this test. The IC_{50} values of the aqueous chamomile extract and gallic acid have been shown in table 2. The plant extract exhibited a good scavenging activity towards DPPH (3.08±0.25 mg/mL). This activity remains lower than gallic acid as standard (0.033±0.0005 mg/mL).

Antinociceptive Activity

The effects of the used plant extract on writhing response in mice are reported in figures 1. The oral administration of the aqueous extracts at doses of 200 and 400 mg/kg caused a significant reduction in the number of the writhing episodes induced by acetic acid compared to the negative control. The percentage of inhibition of the constrictions was calculated as 27.25±23.31% at the dose of 200 mg/kg, 39.60±8.70% at 400 mg/kg, and 90.44±2.80% for the Diclofinac (10 mg/kg) as drug reference. The 400 mg/kg dose caused a significant reduction of the abdominal contortions (P≤0.01) compared to the negative group.

Discussion

Numerous medicinal preparations and the herbal tea of *M. chamomilla* origin have been widely used due to a wide range of their beneficial properties (Kolodziejczyk-czepas et al., 2015). *M. chamomilla* is used in the treatment of many ailments and disorders; internally to facilitate digestion and as antispasmodic, externally to treat minor wounds. In folk medicine, its use spreads from the relief of various pains such as headaches and toothaches to the facilitation of menstruation (Piri et al., 2019). The biological activity of chamomile is associated with its essential oil and phenolic fractions. The major phenolic fraction of chamomile contains flavonoids, their aglycones and/or glycosides, coumarins and phenolic acids (Viapiana et al., 2016). Extraction is the first and crucial step for studying the natural antioxidants from plants (Xu et al., 2017). The result of the present studiy showed that the *M. chamomilla* aqueous extract is rich in polyphenols and flavonoids. These results are close to those found by Sayyar et al. (2018). Many extraction factors play important roles in the extraction efficiency, such as type and concentration of extraction solvent, extraction temperature, extraction time, and extraction pH. Among them, the solvent is one of the most influential factors (Xu et al., 2017; Benchikh et al., 2022). It has also been proven that the quantities and nature of phenolic compounds in plants are related to climatic conditions, altitude and the characteristics of soil (Benabdallah et al., 2020).

Free radicals are thought to contribute to several disorders in the body (Benchikh, 2018). Antioxidants are the agents that can interfere with the oxidation process by various mechanisms, such as, reacting with free radicals, chelating free catalytic metals, and acting as oxygen scavengers (Kumar et al., 2010; Benchikh et al., 2018; Mohammed et al., 2020). In the present study, this plant extract exhibited a good scavenging activity towards DPPH. This is may be due to the high plant contents of polyphenols and flavonoids and its activity towards DPPH radical. It is believed that polyphenols, namely the subfamily of flavonoids, are the most responsible for high antioxidant activity of chamomile (Cvetanović et al., 2018; Mehlous et al., 2020 b).

Analgesic activity of the aqueous extract of *M. chamomilla* was tested by acetic acid induced writhing model in mice. It is well known that acetic acid in some way is responsible for secretion of endogenous mediators of pain there by stimulating the neurons responsible for pain sensation, which are responsive to anti-inflammatory drugs (Gupta et al., 2015). Such pain stimulus leads to the release of free arachidonic acid from the tissue phospholipid. The response is thought to be mediated by peritoneal mast cells, acid sensing ion channels and the

prostaglandin pathway (Miraj et al., 2019; Mamache et al:, 2022). The results of this study have shown that *M. chamomilla* extract can induce analgesia in mice, by inhibiting the acetic mice acid-induced writhing. These results were compared with diclofenac sodium taken as a standard. The extract showed significant activity at 400 mg/kg. In the analgesic activity, primarily by targeting prostaglandins (Kumar et al., 2010). The agent reducing the number of writhing will render analgesic effect preferably by inhibition of prostaglandin synthesis, a peripheral mechanism of pain inhibition (Roy et al., 2019). These results seem to partially justify the folkloric uses of this plant.

Flavonoids and saponins are well known for their ability to inhibit pain perception as well as anti-inflammatory properties due to their inhibitory effects on enzymes involved in the production of the chemical mediator of inflammation (Miraj et al., 2019). The application of antioxidants increases the antioxidative capacity and thus enhances the protection against the consequences of pain. Antioxidants are known to protect central nervous system (Mahendran et al., 2011).

Conclusions

In this work, we reported on the dosage of polyphenols and flavonoids, assessment of antioxidant activity, and *in vivo* analgesic activity of *M. chamomilla* aqueous extract with the aim of valorizing its medicinal use. The present results revealed that *M. chamomilla* aqueous extract is rich in polyphenols and flavonoids and showed a good antioxidant and analgesic activity. These results may explain the effectiveness of its widespread use in traditional medicine as an alternative or supplementary herbal remedy for relieving pain.

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Competing Interests

Authors have declared that no competing interests exist.

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