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Evaluation of Neuropharmacological Activities of Methanolic and Aqueous Extracts of *Citrus Reticulata* (*Rutaceae*) Fruit Peels

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Abstract

Introduction: Herbal medicines are getting more interest because of their cost-effective, eco-friendly attributes and proper reprieve from disease condition. The present study was designed to evaluate the anxiolytic activity potentials in peels of *Citrus reticulata* (Family: *Rutaceae*) in Libya.

Methods: The peel of the fruits were separated and subjected to cold extraction using 99% Methanol and hot water extraction. The extracts obtained were screened for anxiolytic activity of extracts at 1.25 to 5mg/Kg body weight concentrations and were assessed by Elevated Plus Maze.

Results: The results revealed that, both extracts treated animals have shown significant anxiolytic activity. From the results it was evident that *citrus* peel extract of *Citrus reticulata* exhibited significant anxiolytic activity.

Conclusion: From the results it was evident that *Citrus reticulata* has prominent activity in terms of parameters assessed in a dose dependent manner.

Keywords: *Citrus Reticulata;* Anxiolytic Activity; Psychopharmacology

Introduction

Human brain is a speculate and is not explored entirely. It is a multifaceted gathering of interacting neurons and nuclei that control their own and each other's activities in a dynamic manner, usually throughout chemical neurotransmission. Psychopharmacology is the scientific learning of the effect's drugs encompass on mood, thinking, behaviour and sensation. It is different from neuropsychopharmacology, which studies drug-induced alterations in the functioning of cells in the nervous system [1,2]. Two-thirds of the psychotic, depressed, or anxious patients react to the currently available treatments, but the enormity of improvement is not very significant.

The majority of the drugs for these conditions used these days have adverse side effects so the need for better-tolerated, newer and more efficacious treatments is enduring far above the ground [3,4]. The main use of sedative–hypnotic and anxiolytic drugs is to promote calmness (sedatives or anxiolytics) or to create sleep (hypnotics–sedative). Human are exposed to states of restlessness and emotional tension. Anxiety always accompanies many medical and surgical conditions, and it is frequently an indication of psychiatric illness. When the symptoms turn into insufferable or interfere with the treatment of the underlying disease, and if counseling is not enough, drug treatment can be used to help patients manage with their anxiety [5]. There are many medicines are used to treat many psychotherapy and pharmacotherapy illness such as benzodiazepines, azapirones, and antidepressants and others [6].

Citrus reticulata (Rutaceae) is commonly known as narangi or santra (orange). It is a small spiny tree with thick top of slim branches, extensively grown in Egypt, Tunisia and Libya [7]. Mandarin is a collection name for this class of orange with thin, loose

peel. The name 'tangerine might be applied as an interchange name to the entire group, but in trade, it is usually limited to the types with red-orange skin. The fruit has aphrodisiac, laxative, tonic properties and astringent [8,9]. It is also used to alleviate vomiting [10,11]. The fruit peel controls the skin moisture, rough and softens hard skin and possess a cleaning effect on oily skin [12]. Chemical composition of the volatile oil of the fruit peels of this species has been reported [13-17]. The effects of the volatile oil of *C. reticulata* has been studied against *Saccharomyces cerevisiae* [18], pathogenic fungi, *Paenibacillus larvae*, *Schistosoma mansoni*, *Aspergillus flavus*, and other microorganisms [19-24]. The volatile oil of *C. reticulata* also demonstrates the anticancer activity [25-27]. The present paper describes the neuropharmacological Activities of methanolic and aqueous extracts of *Citrus reticulata* (*Rutaceae*) fruit peels of the essential oil of the fruit peel of *C. reticulata* of Tripoli region.

Materials and Methods

Collection of Plant Material and Preparation of Aqueous Extract

The oranges were bought from a shop in Tripoli (February 2019). The *Citrus reticulata* was identified and authenticated by a botanist. Orange rinds were peeled off carefully with the help of a sharp razor blade. Each rind sample was cut into smaller pieces and 30g mass of the sample was taken. The sample was initially rinsed with distilled water. The fresh peels (30g) were added to 30ml hot distilled water. In addition, another 30 g of the fresh peels were macerated in cold 99% methanol for three hours. After 3 hours of maceration at room temperature (28°C), the mixture was then was filtered under vacuum and the filtrate was stored at 4°C and used to treat animals as needed [28].

Experimental Models

Swiss albino mice of either sex weighing about 18–28g (2–2.6-month-old) used for experimental purpose. They were housed in polypropylene cages in the air-conditioned room with the temperature maintained at 25 ± 2°C, and 12h alternating light and dark cycles. The mice were provided with a nutritionally adequate diet and drinking water *ad libitum* throughout the study. Approval by the Animal Ethics Committee for the experimental procedures obtained.

Acute Toxicity Study

Acute toxicity was generally carried out for the determination of LD_{50} value in experimental animals. The aim of performing acute toxicity study is for establishing therapeutic index of a methanolic and aqueous extracts of *Citrus reticulata* and to ensure safety *in-vivo*. Acute toxicity test was performed in mice. All animals were fasted overnight before treatment and were given food one hour after aqueous and methanolic extracts. General behavior was also observed at 0.5, 1, 8, 12 and 24h after administration. The number of animals that died after administration was traced daily for 7 days [29,30].

Elevated Plus-Maze Test

Elevated plus-maze is simple apparatus to study neuroprotective effects [31,32] and anxiolytic responses produced by the test drugs. It is used to test almost all types of anxiolytic agents. Exposure of animals to novel maze alley suggests an approach-avoidance conflict which is stronger in open arm as compared to enclosed arm. Rodents (rats and mice) have an aversion for high and open space and prefer enclosed arm, consequently, spend a greater amount of time in enclosed arm. When animals enter open arm, they freeze, become immobile, defecate and show fear-like movements [33].

The cortisol plasma level is increased, as a true reflection of anxiety. Major advantages of this test procedure are:

a) It is less time consuming, simple and quick

b) no noxious stimuli (light or sound) or prior training is required, and

c) it is conventional and consistent procedure for studying anxiety response as well as anxiolytic action of drug [34,35]. Animals were weighed, numbered, and divided into five groups, each consisting 6 mice. One group was used as control (saline), second for standard drug (diazepam) treatment; groups 3-6 for aqueous *Citrus reticulata* extract treatment (1.25, 2.5, 3.75, 5.00mg/kg, intra-peritoneally) and groups 7-10 for methanolic *Citrus reticulata* extract treatment (1.25, 2.5, 3.75, 5.00mg/kg, intra-peritoneally). Animals were placed individually in the center of the maze, head facing toward open arm and stopwatch was started.

The following parameters were noted for 5 min.

a) First favorite of mouse to open or closed arm.

b) Number of entries in open arm (an arm entry defined as the entry of four paws into the arm).

c) Average time each animal spends in open arm (Average time = total duration in the arm/number of entries) was estimated. Saline and diazepam were injected to the control and standard groups respectively. *Citrus reticulata* extracts were injected to the test groups. After thirty minutes, animals were located individually in the center of the maze. Lastly, a comparison of the preference of the animals to open or enclosed arm, average time spent in open arm and the number of entries in open arm in each group were determined and recorded [36].

Statistical analysis

Data were expressed by mean ± standard error mean. For comparison among the groups, we used analysis of variance with multiple comparisons by post-hoc Dunnett t-test method. The statistical significance of differences between the control and experimental groups was assessed by Dunnett's two-sided t-tests (post-hoc tests). Statistical analysis was done using Statistical Package for the Social Sciences for windows (version 17.0, SPSS Inc., Chicago., USA). Statistical significance was considered $P < 0.05$ level.

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Results

Acute Toxicity Study

With the growing amount of research about naringin as a component of the orange and its potential utilize within the pharmacological and food industries, illuminating its toxicological outline becomes increasingly significant. In the present study, the *Citrus reticulata* extracts were found to be safe up to 200mg/kg orally. This present study is compared with other previous studies in which an oral single dose of 16g/kg of naringin did not produce acute oral toxicity in rats [37]. (Tables 1 & 2) summarized the number of entries (open and total) of mice in elevated plus maze and the time spent by mice on elevated plus maze in open and closed arms, respectively.

Table 1: The number of entries (open and total) of mice in elevated plus maze.

Mean±SEM						
Group	Number of Entries in Open Arm		Total Entries		Percentage Ratio of Open/ Total Arms Entry	
	Aqueous Extract	Methanolic Extract	Aqueous Extract	Methanolic Extract	Aqueous Extract	Methanolic Extract
Control	7.02±0.23	7.02±0.23	33.20±1.02	33.20±1.02	21	21
Diazepam	39.14±0.85	39.14±0.85	50.23±0.35	50.23±0.35	78	78
Citrus reticulata 1.25mg/kg	20.03±2.01	22.04±1.01	40.2±0.23	41.2±0.26	50	53
Citrus reticulata 2.50mg/kg	23.0±0.96	24.0±1.02	42.02±0.38	43.05±0.38	55	56
Citrus reticulata 3.75mg/kg	28.5±0.35	30.4±0.85	44.02±1.23	46.02±0.83	65	66
Citrus reticulata 5.00mg/kg	35.30±0.45	36.30±1.01	49.23±1.36	50.33±1.26	72	72

Table 2: The time spent by mice on elevated plus maze in open and closed arms.

Mean±SEM						
Group	Time Spent in Open Arm in Seconds		Time Spent in Close Arm in Seconds		Percentage Ratio of Open/ Total Arms Entry	
	Aqueous Extract	Methanolic Extract	Aqueous Extract	Methanolic Extract	Aqueous Extract	Methanolic Extract
Control	35.02±0.24	35.02±0.24	260.23±2.03	260.23±2.03	21	21
Diazepam	130.04±1.23	130.04±1.23	160.23±2.34	160.23±2.34	78	78
Citrus reticulata 1.25mg/kg	85.03±1.23	88.03±1.30	230.0±1.35	220.0±1.45	50	53
Citrus reticulata 2.50mg/kg	92.0±0.95	95.0±1.02	204.32±1.11	190.32±2.11	55	56
Citrus reticulata 3.75mg/kg	98.5±1.02	102.5±0.92	175.32±2.35	160.32±3.25	65	66
Citrus reticulata 5.00mg/kg	106.30±1.45	116.30±2.45	140.23±2.35	131.22±1.35	72	72

Discussion

Recently, interests in powerful pharmacological properties and clinical applications of natural products for replacing synthetic drugs are rising. Despite of chief scientific and technological development in combinatorial chemistry, drugs obtained from natural products still create a huge contribution to drug discovery today. The *citrus* plant belongs to the family *Rutaceae*, comprising of about seventeen species found all over the tropical, subtropical and temperate regions [38,39]. Among the species, *Citrus indica*, *Citrus ichangenesis Citrus latipes*, *Citrus megaloxycarpa*, *Citrus macroptera, Citrus jambhiri*, *Citrus aurantium*, and *Citrus reticulate* are the most common. The genus *citrus* includes special essential fruits such as orange, mandarins, limes, lemons, and citrons grapefruits [38]. Even though, there are many groups of plants that are crucial in phytochemistry, *citrus* plantation has been assumed to be a valuable target for commercial agricultural and industrial practices in the world [40]. About 37 major components were identified from *Citrus reticulata* [41,42], and the major components were geranial (19.0%), geranyl acetate (3.9%), limonene (46.7%), neral (14.5%), nerol (2.3), β-caryophyllene (2.6), citronellal (1.3%), geraniol (3.5%), and neryl acetate (1.1%). *Citrus* oil also composed of aldehydes and esters being the lowest percentage components and about 97% monoterpenes with alcohols, with values ranging between 1.8 to 2.2%. It has been reported that the identify of about 16-27 chemical constituents in the peel essential oil of *C. reticulate* was allocated including limonin and naringin and others [43-46].

Naringin is found in many plants. It is a flavonoid and was believed to relieve anxiety at the dose level below 3mg/kg when given intra-peritoneally. At high doses it has been reported to cause sedation but no muscle relaxant property [47]. The anxiolytic effect of naringin has been studies using mice 6-8 weeks old and 30g to 35g weight and the anxiolytic effect was confirmed using elevated plus maze and locomotors activity and these results are in consistency with the results obtained in (Table 1 & 2) [47] It has been reported that the diazepam 2 and 10mg/kg dose were used which increased the number of open arm entries and percent of time spent in open arm as compared to saline control [47] and these results also are in consistency with the results obtained in (Tables 1 & 2).

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The results obtained in (Tables 1 & 2) are also in agreements with studies done by Marder et al. [48,49], which have shown that naringin flavones (which is the main component of *Citrus reticulata*) at the level of dose 3 to 10mg/kg to have excellent anxiolytic potential with no myorelaxation, sedation, or significant reduction in locomotor activity. It is reported that at high doses of narigine shows increase open arm exploration and decrease locomotor activity as shown from reduction in close arm eateries. Naringin and has anxiolytic and sedative potential at high doses. Naringin at dose 30mg/kg show a slight myorelaxant effect in the horizontal wire test [50]. It has been reported that naringin and its derivatives are mediators of GABA receptors and are supportive in relieving anxiety. This flavonoid also has some other targets such as Human Ether-a-go-go-Related Gene (hERG) voltage-dependent potassium channels and Inwardly Rectifying Potassium Channels (GIRK). This flavonoid has positive modulating effect on GIRK channels [51].

Conclusion

The present study demonstrated that the aqueous extract of peeled *Citrus reticulata* possess dose-dependent anxiolytic activity. Further, there is need to isolate, characterize, and screen the active principles that are responsible for its anxiolytic activity. Furthermore, there is need to find out the exact mechanism by which the *Citrus reticulata* extract exerts above effects. Further studies are needed to separate and confirm the active components and its effect on anxiety.

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