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Ethnobotanical study of medicinal plants used for cancer treatment at the province of Nador, Morocco

[Ethnobotanical study of medicinal plants used for cancer treatment at the province of Nador, Morocco]

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Abstract: Morocco has varied wealth of aromatic and medicinal plants (AMPs) which are commonly used for prevention and treatment of various diseases or as complementary therapy such for cancer diseases. An ethnobotanical study was carried out in the province of Nador, located northeast of Morocco. A total of 418 persons were interviewed, information about their profile, type of medicinal plants existing in this area, plant characteristics and uses of those existing plants. Results showed 35 species distributed in 23 families, the most represented were Lamiaceae (7), Apiaceae (5) and Fabaceae (3). This study revealed that the population mainly used seeds (28%), leaves (26%), aerial parts (20%) and fruits (14%). Moreover, it has shown that Nerium oleander were used by the local population for cancer treatments. Biological activity of *N. oleander* showed an antimicrobial effect on *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Keywords: Antioxidant; Antimicrobial; Cytotoxicity; Nerium oleander; Therapy.

Resumen: Marruecos tiene una riqueza vegetal muy variada de plantas aromáticas y medicinales (AMP) y se utilizan comúnmente para la prevención y el tratamiento de diversas enfermedades o como terapia complementaria, como las enfermedades del cáncer. Se llevó a cabo un estudio etnobotánico en la provincia de Nador, situada al noreste de Marruecos. Se entrevistó a un total de 418 personas, información sobre su perfil, tipo de plantas medicinales existentes en esta zona, características de las plantas, usos de las plantas existentes, etc. Los resultados mostraron una alta riqueza de especies de 35 especies distribuidas en 23 familias, las más representadas fueron Lamiaceae (7), Apiaceae (5) y Fabaceae (3). Este estudio reveló que la población utilizó preferentemente semillas (28%), hojas (26%), partes aéreas (20%) y frutos (14%). Además, se ha demostrado que la población local utilizaba Nerium oleander para tratamientos contra el cáncer. La actividad biológica de *N. oleander* mostró un efecto antimicrobiano sobre *Escherichia coli*, *Pseudomonas aeruginosa* y *Staphylococcus aureus*.

Palabras clave: Antioxidante; Antimicrobial; Citotoxicidad; Nerium oleander; Therapy.

INTRODUCTION

Since antiquity, humans have used aromatic and medicinal plants (AMPs) for the treatment of many diseases (Petrovska, 2012; Bouarourou *et al*., 2019). The oldest written evidence about the use of plants for the preparation of medicines was found on a Sumerian clay slab in Nagpur, 5000 years ago (Kelly, 2009). There is growing interest in the use of herbal medicines, especially over the past decade (Li *et al*., 2019). About 50% of the population of many industrialized countries use AMPs (Fisher & Ward, 1994; MacLennan *et al*., 1996; Eisenberg *et al*., 1998; Ekor, 2014; Cumali, 2018), this rate is even higher in developing countries and reaches 80% in some African countries (Bannerman *et al*., 1983; Zhang, 2002). This renewed interest in medication by AMPs can be partly explained by the deficiency of modern medication, especially in developing countries (Payyappallimana, 2010), and also by the interest of the use of alternative medical health care in order to reduce the side effects of certain conventional drugs found in the market, particularly in the case for cancer disease (Cassileth & Deng, 2004).

Cancer is considered among the main causes of morbidity in the world (Wang *et al*., 2020), it corresponds to an uncontrolled proliferation of cells indoor the body. In fact, cancer is triggered by genetic mutations in DNA that will transform natural cells (Bignell *et al*., 2010); the resulting cells reproduce abnormally, ignoring growth regulation signals. Cancer cells thus acquire an invasive character and cause changes in the surrounding tissues (Brunner *et al*., 2010). Chemotherapy is widely prescribed for the fight against cancer, it relies on the use of drugs to kill or inhibit the growth of cancerous cells as well as healthy ones that have a high proliferative potential (Dickens & Ahmed, 2018). Due to this non-selectivity, various side effects are associated with chemotherapy such as anemia, thrombocytopenia, leucopenia, vomiting, stomatitis, and diarrhea (Love *et al*., 1989). To reduce the toxic effects of chemotherapy, researchers have used molecules from natural origin (Schirrmacher, 2019). Certainly, more than 60% of the anti-cancer compounds used are obtained from plant, marine and microbial sources (Kooti *et al*., 2017).

Most investigations on AMPs are based on the traditional knowledge of cultures and civilizations and this traditional know-how constitutes a source of valuable information. Morocco is one of the countries in the Mediterranean area having a long medical tradition based on medicinal plants (Myers & Cowling, 1999). Traditional medicine has always occupied an important place in the traditions of medication in Morocco; the province of Nador, rich in its floristic diversity. Our work constitutes a contribution to the survey of plants used in traditional medicine in this region. A particular interest is carried to those used by the population for the treatment of cancer. Also, the study of their cytotoxic and antimicrobial properties will make it possible to explain their biological effect in order to validate these medical practices but also the danger which can present to the user.

MATERIALS AND METHODS

Ethnobotanical study

Study area

The Province of Nador is located at the northeast of Morocco, on the coast of the Mediterranean Sea (35°10'7.019"N2°55'39.301"W). Its Mediterranean climate with contrasting seasons but characterized by an arid to semi-arid regime. Rainfall in the province of Nador is around 150 to 450 mm/year and average temperatures are around 13°C in winter and 26°C in summer (Irzi, 2002). The province abounds in floristic wealth concentrated mainly at the level of the Marchica lagoon and Mount Gourougou, in particular the forest of Tazouda on the Massif of Gourougou has an area of 4000 ha, and the forest of Jbel Bayou (35°13'41.5"N 2°58'03.6"W) between the two cities of Nador and Beni Nsar.

Data collection

The ethnobotanical survey was carried out during the period from September 2018 to February 2019. A questionnaire was set up to collect data on the individuals questioned (sex, age, level of study, family situation and socio-economic level) as well as data on ethnopharmacological plants used in the treatment of different diseases in particular cancer (scientific name, common name, common name, parts used and mode of preparation). The plant species were identified using observation of species in field and matching with a data base of plant species. Also, they were identified according to the survey with local population. The sampling was random, and the dialogue was realized in Amazigh or Arabic languages depending on the case. The 418 respondents were informed of the purpose of this study.

Biological activities of Nerium oleander
Extraction of essential oil

After drying at room temperature and away from direct sunlight, the leaves and stems of N. oleander were crushed before being extracted by cold soaking with methanol, repeated until exhaustion, followed by filtration. The filtrate was concentrated using a rotary steamer (60°C). The extract obtained was stored in opaque flasks in the dark and at a temperature of 4°C, until analysis of the cytotoxic activity.

Antimicrobial activity

The antimicrobial activity of the aqueous extract from the leaves and stems of N. oleander was determined using the agar diffusion method (Jacob et al., 1979). Three bacterial strains were tested: two Gram negative (Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853) and one Gram positive (Staphylococcus aureus ATCC 25923).

A microbial suspension of 108 UFC/mL was used for the inoculation of Petri dishes containing Mueller Hinton agar. Sterile disks 6 mm in diameter were impregnated with 10 µL of essential oil and then placed on the inoculated dishes. The latter were placed at 4°C for 2 to 4 h and then incubated at 37°C. The antimicrobial activity was determined by measuring the diameters of the zones of inhibition around the discs, all the tests were carried out in triplicate.

Cytotoxic activity

The cytotoxic activity of the extracts of the vegetative organs (stem and leaf) of N. oleander was carried out by the biotest of A. saline. In 48-well plates, at least five larvae were deposited per well containing 1 ml of crude N. oleander essential oil and a 1/2 dilution. The plates were then incubated at 30°C. The mortality of the larvae was determined after 24 h and data were analyzed after being corrected using Abbott's formula (1925), expressed as follows (Eq. 1):

$$Mc = [(A-B)/G] \times 100 \quad \text{(Eq. 1)}$$

M = Corrected mortality; A = Number of dead larvae after treatment; B = Number of dead larvae in the controls and G = the total number of larvae tested.

Data analysis

The data collected following the surveys were processed using Microsoft Excel software. The citation frequency (F) was calculated using the formula (Eq. 2):

$$F = (n/N) \times 100 \quad \text{(Eq. 2)}$$

n: the number of respondents who mentioned the species; N: the total number of respondents.

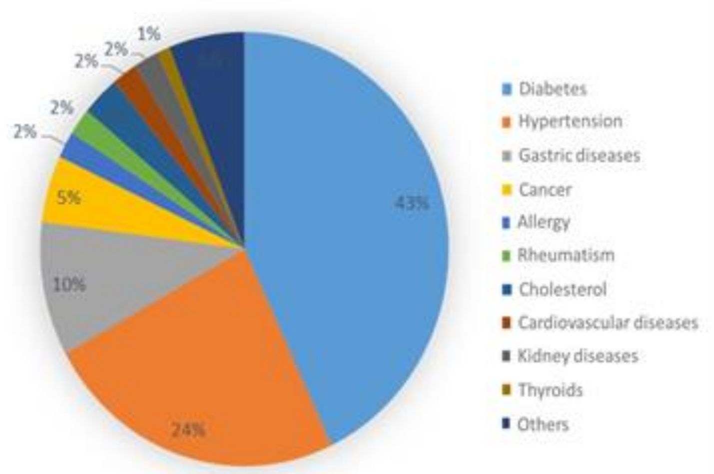

Figure No. 1
Distribution of the different diseases in the population studied

RESULTS AND DISCUSSION

Medicinal plants used according to the survey

From the 418 people surveyed randomly, 70% use modern medicine, while 21% use traditional medicine and 9% combine both of them. The study of the distribution of diseases showed a predominance of diabetes (40%), hypertension (21%) and digestive diseases (10%) (Figure No. 1). In addition, cancer affects 5% of the population studied, which remains high compared to the overall standardized incidence of 102 affected by cancer per 100,000 inhabitants per year (RCRC, 2017).

Frequency use of medicinal plants according to the survey profiles: Gender use

Aromatic and medicinal plants are used by both sexes, however there is a dominance of women (87%) compared to men (13%). This female dominance has also been reported by other ethnobotanical work carried out in different regions of Morocco, whose frequencies obtained vary from 53 to 75% (Eddouks *et al*., 2002; Tahraoui *et al*., 2007; Benlamdini *et al*., 2014; Hayat *et al*., 2020). This can be explained by the fact that women usually are more attached to traditional knowledge on medicinal species and their different therapeutic uses (Jouad *et al*., 2001).

Age group

In this province, the old people use the AMPs more than the youngest. Also, 22% of the population studied belong to the age group (50-59 years), followed by the age groups (60-69) with 20% and those over 70 years' old which represent a frequency of 20%. Finally, followed by those of (40-49), (30-39), (20-29) and (10-19) with respectively 19%, 11%, 6% and 2% (Figure No. 2a).

Ethnobotanical knowledge was generally acquired through long experience accumulated and transmitted from one generation to another (Benlamdini *et al*., 2014). The results obtained confirm the fact that the old people have more knowledge of traditional herbal medicine compared to other age groups. On the other hand, young people under 30 tend to no longer believe too much in this traditional medicine (Eddouks *et al*., 2002).

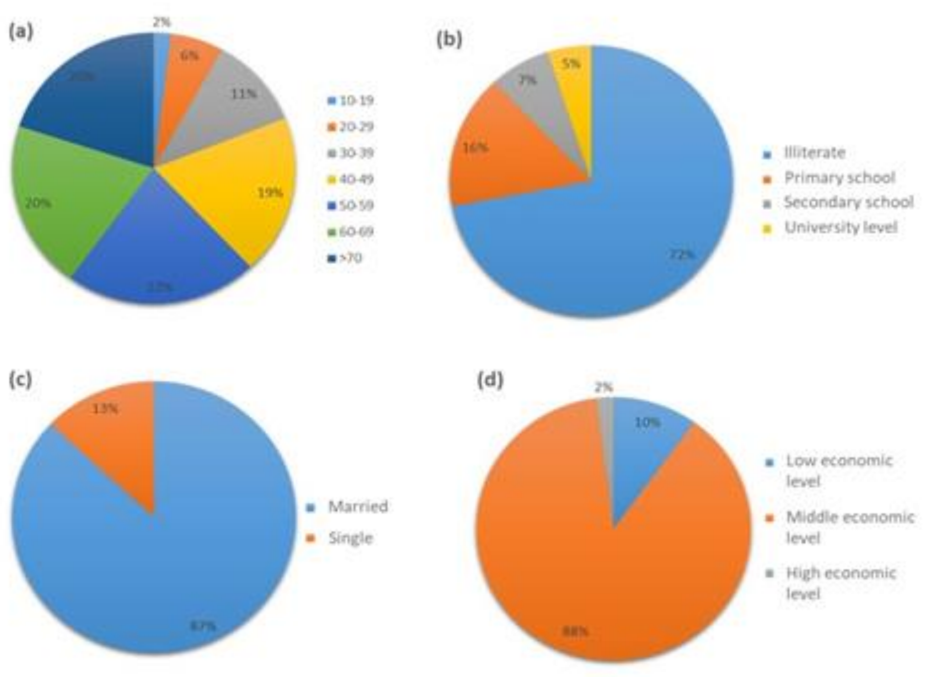

Figure No. 2
Distribution (%) of AMPs use by: (a) Age; (b) Level of study; (c) Family status; (d) socio-economic level

Education level

The frequency use of AMPs was inversely related to the level of education of users. The vast majority of users (72%) are uneducated, while 16% have a primary level, 7% have a secondary level. Moreover, academics used very few AMPs with a frequency of 5% (Figure No. 2b). These results support those obtained by other authors (Mehdioui & Kahouadji, 2007; Benlamdini *et al*., 2014; Hayat *et al*., 2020).

The family situation

Medicinal plants are requested more by married people (87%) than by single people (13%) (Figure No. 2b). This can be explained by the influence of women in couples (Bouzid *et al*., 2017).

The socio-economic level

The results of this study show that people with middle class level use AMPs more often (88%), followed by those with a low level (10%) and finally users with a high lifestyle level who only represent 2% (Figure No. 2c). This could be explained by the fact that families try to reduce the high load price of medical care (Hayat *et al*., 2020).

The ethnobotanical survey conducted in the case of this study made it possible to identify the list of medicinal plants used by the population in Nador region. For each plant, information about the following parameters were presented in Table No. 1: family, nomenclature (scientific name, common name, local name), part used, mode of preparation and frequency of use.

Table No. 1
List of medicinal and aromatic plants identified in the Nador region and their frequency of mention

Family	Scientific name	Common name	Local name	Part used	Preparation mode	F
Amaryllidaceae	*Allium sativum*	Garlic	Touma	Fruit	Others	9,77
Asteraceae	*Artemisia herba alba*	Mugwort white	Chih	Aerial part	Infusion	2,26
Brassicaceae	*Lepidium sativum*	Crespinette	Hab rechade	Fruit	Infusion	1,50
	Medicago sativa	Alfalfa	Fassa	Seed	Powder	0,75
Fabaceae	*Cassia acutifolia*	Senna	Sana	Leaf	Infusion	0,75
	Trigonella foenumgraecum	Fenugreek	Halba	Seed	Poudre	4,51
	Lavandula officinalis	lavender	Khezama	Leaf	Infusion	3,01
	Origanum compactum	Marjoram	Mredoudech	Aerial part	Infusion	1,50
	Rosmarinus officinalis	Rosmary	Azir	Aerial part	Infusion	11,28
Lamiaceae	*Origanum compactum*	Oregano	Zaatar	Aerial part	Infusion	3,76
	Salvia officinalis	Sage	Salmia	Aerial part	Infusion	3,01
	Mentha pelugium	Pennyroyal mint	Flio	Aerial part	Infusion	1,50
	Ajuga iva	Ivet musk	Chandgoura	Leaf	Infusion	0,75
Ranunculaceae	*Nigella saliva*	Nigella	Sanouj	Seed	Powder	0,75
Solanaceae	*Populus nigra*	Black poplar	Safsaf	Leaf	Decoction	1,50
Xanthorrhoeaceae	*Aloysia triphylla*	Verbena	louiza	Leaf	Infusion	8,27
Zingiberaceae	*Zingiber officinalis*	Ginger	Zanjabil	Rhizome	Powder	6,02
Apocynaceae	*Nerium oleander*	Oleander	Defla	Leaf	Smoking	1,50
Robiaceae	*Rubia tinctorum*	Madder of the dyers	Fowa	Rhizome	Powder	0,75
Punicaceae	*Punica granatum*	Grenadier	Roman	Fruit (Peel)	Powder	0,75
Linacaea	*Linum usitatissimum*	Cultivated flax	Kettan	Seed	Powder	1,50
Poaceae	*Triticum turgidum*	Durum wheat	Zraâ	Seed	Maceration	0,75
Schisandraceae	*Ilicium verum*	Chinese star anise	Badian	Seed	Infusion	0,75
	Carum carvi	Caraway	Krawia	Seed	Infusion	2,26
	Cuminum cyminum	Cumin	Kamoun	Seed	Powder	3,76
Apiaceae	*Foelniaulum vulgare*	Fennel	Nafaâ	Fruit	Infusion	3,01
	Petroselinum sativum	Parsley	Maâdnous	Aerial part	Infusion	2,26
	Pimpinella anisum	Green anise	Habat hlawa	Fruit	Maceration	1,50

Myrtaceae	*Eugenia caryophyllata*	Clove	Kronfel	Flower	Infusion	0,75
Oleaceae	*Olea europaea*	Oleaster	Zitoun	Leaf	Infusion	11,28
Rosaceae	*Rubus idaeus*	Raspberry bush	Toute	Leaf	Infusion	0,75
Lauraceae	*Cinnamomum verum*	Ceylon cinnamon	Karfa	Dried spread	Infusion	4,51
Cupressaceae	*Tetraclinis articulata*	Thuja	El arar	Leaf	Powder	0,75
Zygophyllaceae	*Peganum harmala*	wild street	Harmel	Seed	Powder	1,50
Capparaceae	*Capparis spinosa*	Caper	Cabar	Seed	Powder	0,75

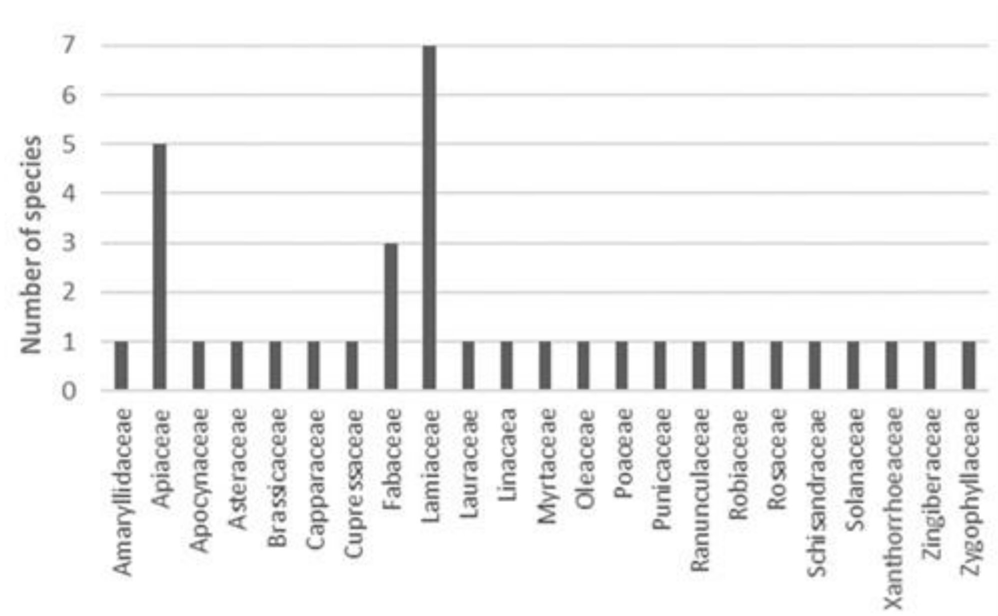

Figure No. 3
Number of species listed by botanical family, founded in this survey study

Floristic analysis
The results obtained allowed the counting of the existing 35 species belonging to 23 botanical families. There was a predominance of the Lamiaceae family with 7 listed species followed by the Apiaceae with 5 species and the Fabaceae with 3 species. However, the other families listed are presented with only one species (Figure No. 3).

Part used of the plant
AMPs have various therapeutic properties, they can be used in whole or in part (leaf, stem, flower, root, etc.). In this study area, 28%, 26%, 20% and 14% of the population preferentially uses the seeds, the leaves, the aerial part and the fruits, respectively. Still, the rhizomes, dried bark and flowers are the least exploited parts (Figure No. 4).

Mode of preparation
According to this survey, AMPs could be prepared in different ways, infusion is the most predominant mode of preparation with 54%, followed by powder preparation 31%, then maceration 6%. The other methods of preparation remained little used (Figure No. 5).

Plants used against cancer
The ethnobotanical survey carried out made it possible to identify the plants used in the treatment of cancer. The study of the antimicrobial and cytotoxic activities of N. oleander were carried out in order to verify the relevance of ancestral knowledge and to estimate the advantages and risks of this practice.

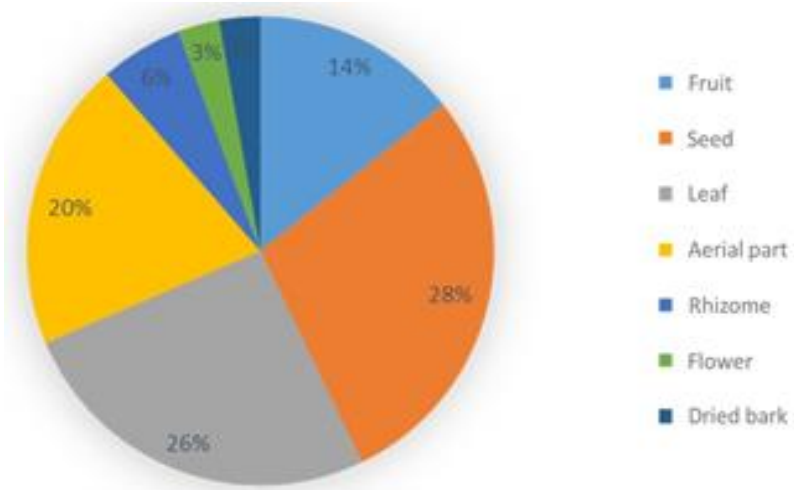

Figure No. 4
Percentage of different parts used in herbal medicine for 418 people surveyed

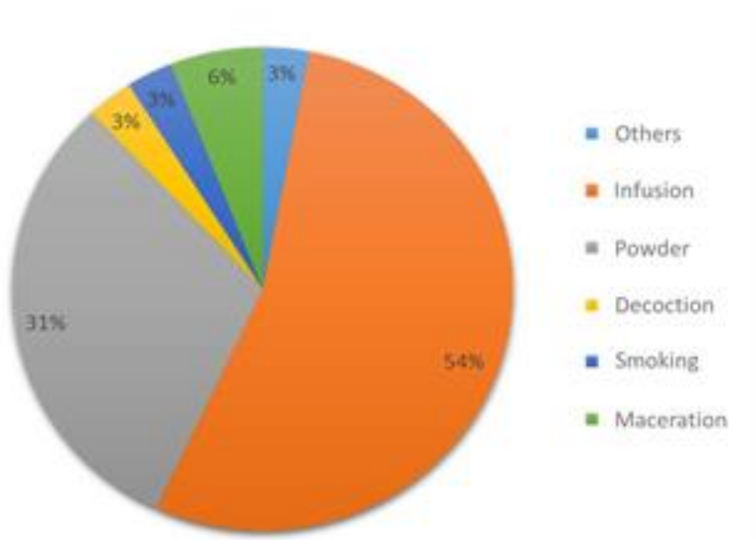

Figure No. 5
Attribution (%) of the plant preparation mode for the users surveyed in this study

Antimicrobial activity of N. oleander

The disk diffusion method showed that *N. oleander* exhibits antimicrobial activity and that the latter varies according to the bacteria tested. The results indicated that the aqueous extract was active on *E. coli*, *P. aeruginosa* and *S. aureus* strains with an inhibition zone diameter reaching respectively (21 ± 1.2) mm, (14.5± 0 .6) mm and (7.75 ± 0.7) mm. These results are similar to those reported by several authors (Derwich *et al*., 2010; El Sawi *et al*., 2010; Mouhcine *et al*., 2019). Moreover, antimicrobial activity might be due to a wide variety of secondary metabolites, such as tannins, terpenoids, alkaloids and flavonoids (Cowan, 1999).

Artemia salina biotest

The results of corrected mortality (Mc) of the larvae of *A. salina* are presented in Table No. 2. The aqueous extract of the leaves and stems of *N. oleander* caused respectively a mortality of around 100% and 15.08%. A concentration-cytotoxicity effect was also noted for the leaf extracts, since the ½ dilution of the extract gave a Mc of the order of 12.97%. While the same dilution of stem extracts didn't have any effect. This testifies that the majority of the activity is at the level of the leaves. These results are similar to those reported by Siddiqui *et al*., 2012.

Table No. 2
Average mortality corrected for the biotest of *A. saline*

Part of the plant	Concentration	Corrected mortality (%)	Standard deviation
Leaf	Raw extract	100	0
	Dilution ½	12,97	4,72
Stem	Raw extract	15,08	5,29
	Dilution ½	0	0

The cytotoxicity of N. oleander extracts is mainly due to the production of secondary metabolites, in particular cardiac glycosides (Radford *et al*., 1986). These molecules are known for their anticancer activity (Newman *et al*., 2007). Also, Oleandrin is considered one of the main cardiotonic glycosides produced by *N. oleander.* This bioactive compound has remarkable pharmacotherapeutic potential as anticancer, anti-inflammatory, anti-HIV, neuroprotective, antimicrobial and antioxidant (Kumar *et al*., 2013; Mouhcine *et al*., 2019; Kanwal *et al*., 2020). (Table No. 2).

CONCLUSION

Phytotherapy is an important source of medication in the province of Nador. This ethnobotanical survey has made it possible to report the floristic abundance of the region as well as the traditional knowledge transmitted from generations by the local populations. Particular interest has been taken in the study of medicinal plants used in the treatment of cancer. It appears that the species N. oleander has been widely used by the population of this region. The presence of antimicrobial and cytotoxic activity in N. oleander could be beneficial in the treatment of cancer. The high toxicity of the leaves can have side effects. In-depth studies will be necessary to highlight this empirical knowledge which is a natural and cultural heritage.

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