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Role of Catecholamine's Compounds in Anti-Inflammatory and Antioxidant of Two Plants *Santolina chamaecyparissus* and *Launaea mucronata*

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Abstract: Natural products have long been a thriving source for the discovery of new drugs because of their chemical diversity. The study was designed to investigate the anti-inflammatory, antioxidant and composition of methanol extract and alkaloid fraction of two plant family asteraceae, *Santolina chamaecyparissus* and *Launaea mucronata* growing in desert habitat of North Region. The Anti-inflammatory of plant extracts using carrageenan induced paw edema (200 mg/kg) of extracts were tested, Santolina *chamaecyparissus* showed high inhibition after four hour. DPPH radical scavenging activity of various leaf extracts of Launaea and Santolina were tested, all the extracts showed different levels of DPPH radical scavenging activity over the range of 2-10 mg/ml concentration, the EC50 values of MeOH extracts and alkaloid fraction of Launaea and Santolina were 27.85, 30.55 25.94 and 32.22 mg/ml, respectively. The Fluoroatropine, Aspidofractinine-3-methanol and Dehydroabietic acid are the main constituents of the extracts which investigated by capillary GC and GC-MS. The role of the identified compounds in inflammatory inhibition was discussed.

Key words: Anti-inflammatory, catecholamines, aspidofractinine-3-methanol, fluoroatropine *Launaea mucronata*, *Santolina chamaecyparissus* and carrageenan induced paw edema method

INTRODUCTION

Natural products are often a source for bioactive compounds which have great potential for developing novel therapeutic agents.

The inflammatory response starts with signal recognition that may have an infectious or inflammatory origin and the release of chemicals from tissues and migrating cells called mediators (Blancas *et al*., 2010). The list of these mediators includes amines like histamine and 5-hydroxytryptamine, bradykinin, (representing short peptides), long peptides such as interleukin-1 (IL-1), lipids such as prostaglandins (PGs) and leukotrienes (LTs) and enzymes *rcentage inhibition*. Pain is mainly a defensive mechanism of the body and is an ill-defined, unpleasant sensation and emotional experience along with acute or chronic tissue damage which is usually induced by an external or internal noxious stimuli (Li and Vederas, 2009; Cechinel Filho and Yunes, 1998). The subsequent elaboration of mediators such as interleukin-1 and tumor necrosis factor-TNF-α is believed to propagate the synthesis, release and action of autacoid prostaglandin E2 (PGE2) and F2α by the endothelium and pericytes of brain capillaries that excite pain nerve endings (Talib and Mahasneh, 2010). The increase in prostaglandin levels within the peritoneal cavity increases capillary permeability and thus enhances inflammatory pain (Ezell *et al*., 2010).

In this study, two medicinal plants *Santolina chamaecyparissus* and *Launaea mucronata* were collected from North region of Saudi Arabia (Arar) in the Spring season (2013). They were extracted successively by methanol for studding the anti-inflammatory activity using Carrageenin-induced paw edema method. Searching for new natural anti-inflammatory and antioxidant drugs.

Genus *Launaea* is a relatively small genus consists of about 40 plant species growing in dry, saline and sandy habitats. They belong to the tribe Lactuceae of the family Asteraceae (Ozenda, 2004). Several species of this genus are used in folk medicine in bitter stomachic, skin diseases and reported to have antitumor, insecticide and cytotoxic activities (Rashid *et al*., 2000). The antimicrobial activities of coumarin constituents also studied (Abdu *et al*., 2007).

Santolina spp (Asteraceae family, tribe Anthemideae) are widely used in traditional medicine for their anti-inflammatory properties. Various germacrene derivatives and coumarins with antiphlogistic activities have previously been isolated from plants of this genus (Sala *et al*., 2000). *Santolina chamaecyparissus* (Genn. ex Fiori) Arrigoni is an endemic shrub has been used in folk medicine as an intestinal vermifuge against horse strongyloidiasis and as a parasite repellent. The anti HSV-1 and anti HSV-2 activity of the essential oil and the

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chemical composition of the acetone extract from the aerial parts of S. *chamaecyparissus* have studied (Filippo Cottigliaa *et al*., 2005).

MATERIALS AND METHODS

Plant material: Flowering aerial parts of *Launeae* mucronata and Santolina *chamaecyparissus* were collected from wild population growing in the Arar/Rafh road, Northern Region (Arar), Saudi Arabia in April 2013, the identity of the plants have been kindly verified by Prof. Dr. A. Kamal, Faculty of Science, Northern Border University. Voucher specimens were deposited in the herbarium of faculty of science, Northern Border University, girl department.

Extraction and purification: The air-dried powder of plant (100 g of each plant) was extracted by percolation in 90% methanol and filtered off; the marc lifted was extracted by the same way (this process repeated four times). The combined methanol extracts were concentrated under reduced pressure at temperature not exceeding 40°C till dryness. The extracts were subjected to various phytochemical tests and showed the presence of alkaloids, steroids and glycosides.

Crude methanolic plant extract (20 g) of each plant were successively defatted with petroleum ether (200 ml) and filtered. The air-dried residue was washed successively with methanol (100 ml) and filtered, to the residue, water (10 ml) and HCl (2 N, 10 ml) were added, stirred and methylene chloride (200 ml) was added to extracts, tannins, flavonoid and other compound separated in neutral layer. The aqueous layer was neutralized by adding 10% Na_2CO_3 (10 ml) solution and kept for 2 days in a freezer and filtered. The solid fraction (12 and 8 g)of *Launaea* and *Santolina* respectively, the separated fractions were tested for the presence of alkaloids by chemical tests (alkaloid fraction, gave positive test for Meyers reagent and Wagner reagent).

The neutral fraction were s separated and concentrated to dryness to provide the gummy residue (5 and 3 g), which gave negative test for alkaloids (non-alkaloid fraction).

Thin-layer chromatography: Thin-layer chromatography was carried out on silica gel coated plates (20 x 20 cm, 0.25 mm layer) in the system:CHCl3: BuOH:conc NH_4OH (50:50:2.5). After elution, the residue of ammonia was removed by careful drying in a heated oven. The plates were sprayed with ninhydrin reagent (purple colour with mescaline, rf value 0.46) and iodoplatinate Dragendorff's reagent (brownish-purple colour with mescaline) (Lum and Lebish, 1974).

To 100 mg of each of the two samples, 3 ml of 10% HCl was added in an Erlenmeyer flask and the flasks immersed in a boiling water bath for 15 min. The solutions were filtered through Whatman No. 1 filter paper and the residues were washed with 10 ml distilled H_2O. The filtrates were then extracted three times with Et2O (20 ml). The resulting emulsions were centrifuged at 1500 rpm. The ether layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness to give 1.99 mg (2%) and 1.95 mg (2%), respectively, of the alkaloid fraction. The alkaloid extracts were tested with Dragendorff's reagent using Whatman No. 1 filter paper.

All these fractions were kept in a desiccators and stored in a freezer till the conduct of experiments. The alkaloid fraction of *Launeae* plant was subject to column chromatography afforded five important fractions, one of them are pure compound, All fractions were identified by GC-MS, also non-alkaloid fraction of two plants were analysis by GC-MS (Witte *et al*., 1987; Ionkova *et al*., 1994).

GC-MS analysis: The GC-MS analysis of both extracts was performed using GC-M SHIMADZU MS 2010 instrument equipped with AB innowax column (0.5 x 60 mm id, film thickness 0.25 µm). Initially, oven temperature was maintained at 50 x C for 3 min and temperature was gradually increased up to 280°C at 30 min and 0.2 µl of sample was injected for analysis. Helium was the carrier gas. The flow rate of helium gas was 1.2 ml/min. The sample injector and mass transfer line temperature were set at 270 and the 280°C and split ratio is 20 throughout the experimental periods. The ionization mass spectroscopic analysis was done with 70 eV. Mass spectra were recorded across the range of 40 to 1000 m/z for the duration of 35 min. Identification of components was based on comparison of their mass spectra with those of Wiley and NIST libraries and those described by Adams (1995) as well as on comparison of their retention indices with literature.

Pharmacological studies

DPPH radical scavenging activity: The free radical scavenging activity of the extracts, based on the scavenging activity of the stable 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical was determined by the method described by Braca *et al*. (2001), 0.1 ml different extracts in different concentrations (100 to 8 mg/ml) were added to 3ml of a 0.004% methanol solution of DPPH. Absorbance at 517 nm was determined after 30 min and the percentage inhibition activity was calculated from this Eq.:

$$\frac{A0-A1}{A0}\times 100$$

where, A0 is the observance of the control and A1 is the observance of the extract/ standard (Ascorbic acid).

1-Determination of Median lethal Dose (LD_{50}): The extract dissolved in distilled water then given orally in

graded doses to mice up to 4 g/kg and the control group received the same volume of the vehicle. The percentage mortality was recorded 24 h later. No mortality was occurred after 24 h and according to Semler (Suleyman and Demircan, 2004). So the experimental dose were used in the present study was 1/20 of (4 g/kg) of the all extract (200 mg/kg).

Animals: Wister albino rats of both sex, weighing ranged from 125-150 g and Swiss mice of 20-30 g body weight were used throughout the experiments. Rats were used for determination of the anti-inflammatory activities, while mice were used for determination of the median lethal doses (LD_{50}) and analgesic study. The animals were obtained from the animal house colony of the National research Centre, Dokki, Giza, Egypt. The animals were housed in standard metal cages in an air conditioned room at 22±3°C, 55±5% humidity and provided with standard laboratory diet and water *ad libitum*. Experiments were performed between 9:00 and 15:00 h. All experimental procedures were conducted in accordance with the guide for care and use of laboratory animals and in accordance with the Animal procedures were performed in accordance with the Ethics Committee of the National Research Centre and followed the recommendations of the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 19850).

Anti-inflammatory effects (carrageenan-induced paw oedema assay): Paw oedema was induced by injecting 100 µL of a 1% solution of sterile carrageenan lambda in saline in the subplanter region of the right hind paw of the rat (Winter and Risley, 1962). Carrageenan caused visible redness and pronounced swelling that was well developed by 4 h and persisted for more than 48 h. The rats received vehicle or extract orally 60 min before carrageenan administration. Hind footpad thickness (paw volume) was measured immediately before carrageenan injection and 1-4 h after carrageenan injection by using plethysmometer (UGO Basile 21025 Comerio, Italy). The difference between initial and subsequent readings gave the change in edema volume for the corresponding time. Oedema volume of control (Vc) and volume of treated (Vt) were used to calculate percentage (%) inhibition and (%) edema volume by using following formula:

$$\text{Inhibition (\%)} = 1-\frac{Vt}{Vc}\times 100$$

$$\text{Edema volume (\%)} = 100\times\frac{\text{(Oedema volume after drug treatment)}}{\text{Initial volume}}$$

Rats were divided into six groups each of six. They received orally saline as control, four different extracts (200 mg/kg) and indomethacin (25 mg/kg orally).

Statistical analysis: Values were expressed as means±S.E. Comparisons between means were carried out using one way ANOVA followed by least significant difference (LSD) and Tukey multiple comparisons test. $p<0.05$ was accepted as being significant in all types of statistical tests. SPSS software (version 17) was used to carry out all statistical tests.

RESULTS AND DISCUSSION

Acute toxicity study: Results showed no percentage mortality after 24 h of methanol extracts of two plants, oral administration at graded doses up to a 4 g/kg and according to Semler who reported that if just one dose level at 5 g kg is not lethal, regulatory agencies no longer require the determination of an LD_{50} value. So the experimental doses used were 1/20 of 4 g kg of each extract (200 mg/kg). So LD_{50}, of methanol extracts are 4000 mg (4 g)/kg body weight.

Anti-inflammatory effects (carrageenan-induced paw oedema assay: Carrageenan-induced rat paw oedema is used widely as a working model of inflammation in the search for new anti-inflammatory drug. The anti inflammatory activity of the, methanolic and alkaloid extract of *Launaea and Santolina* were evaluated by carrageenan-induced rat paw oedema method (Winter and Risley, 1962; Adeyemi *et al*., 2002), the results are shown in Table 1. The results showed that the alkaloid fraction of Santolina `with a dose of 200 mg/kg b.w show high inhibition than methanolic extract, while in Launaea each methanolic extract and alkaloid fraction gave the same results.

This result indicated that all extract of Launaea and santolina showed a maximum anti-inflammatory activity as compared to the reference drug indomethacin, The development of odema in the paw of the rat after the injection of carrageenan is due to release of histamine, serotonin and prostaglandin like substances (Vinegar *et al*., 1969). Significantly high anti-inflammatory activity of extracts may be due to inhibition of the mediators of inflammation such as histamine, serotonin and prostaglandin this may be due to the presence of alkaloid compound and nurotransmitant (norepinephrine) which detected in plant extract as a major compound.

The norepinephrine from locus ceruleus cells in addition to its neurotransmitter role locally diffuses from "varicosities". As such, it provides an endogenous anti-inflammatory agent in the micro environment around the neurons, glial cells and blood vessels in the neocortex and hippocampus (Heneka *et al*., 2010). Up to 70% of norepinephrine projecting cells are lost in Alzheimer's Disease. It has been shown that norepinephrine stimulates mouse microglia to suppress Aβ-induced production of cytokines and their phagocytosis of Aβ, suggesting this loss might have a role in causing this

Table 1: Time course of the effect of oral administration of *different* extracts and indomethacin on rat paw oedema

	Time			
Groups	1st H	2nd H	3rd H	4th H
Carrg.	106.06±3.07	149.47±2.54	168.10±3.28	183.57±4.02
Indomethacin	52.48±4.72*	58.25±5.50*	38.86±3.74*	21.51±1.99*
Sc. MeOH	66.72±5.94*	51.48±4.67*	40.01±3.31*	26.10±1.40*
Sc Alkaloid	69.98±6.43*	54.19±5.06*	36.36±3.39*	28.92±1.60*
Lm MeOH	58.75±2.46*	42.21±3.08*	28.97±2.82*	16.40±0.88*
Lm Alkaloid	69.24±4.88*	57.93±5.66	40.58±3.84*	14.07±1.32*

SC: Santolina Methanol Extract, SC: Santolina alkaloid L.m: launaea methanol Lm: Launaea alkaloid

Table 2: Antioxidant activity of plant extracts and ascorbic acid (0.1 M concentration) *in vitro*, using DPPH radical scavenging activity method

Conc. mg/100 g	Santolina MeoH	Santolina alkaloid	Launaea MeOH	Launaea alkaloid
10	30.23	31.75	35.12	39.19
20	37.63	36.26	37.88	39.88
40	43.37	49.35	48.35	45.25
60	45.03	55.55	47.46	47.46
80	47.54	48.09	46.24	48.04
100	49.87	23.12	52.79	50.79

Table 3: Active compounds identified by GC-MS

Santolina chamaecyparissus			*Launaea mucronata*		
Name of compound	Molecular formula	MW	Name of compound	Molecular formula	MW
Quinic acid	$C_7H_{12}O_6$	192	Duroquinone	$C_{10}H_{14}O_2$	166
Hydroqunion	$C_6H_4(OH)_2$	110	Tetrahydroaraucarolone	$C_{20}H_{34}O_4$	334
Zingerone	$C_{11}H_{14}O_3$	194	Menobutone	$C_{15}H_{14}O_4$	258
p-Vinylguaiacol	$C_9H_{10}O_2$	150	Aspidofractinine-3-methanol	$C_{20}H_{26}N_2O$	310
Strophanthidol	$C_{23}H_{34}O_6$	407	Fluoroatropine	$C_{17}H_{22}FNO_3$	307
Beta Damascone	$C_{13}H_{20}O$	192	DL-Norepinephrine	$C_8H_{11}NO_3$	169
Ambreinolide	$C_{17}H_{28}O_2$	264.4	Epinephrine	$C_9H_{13}NO_3$	183
(E)-Nuciferol	$C_{15}H_{22}O$	218	Allo-4-hydroxy-d-prolylglycine	$C_7H_{12}N$	204
Dehydroxy-isocalamendiol	$C_{15}H_{24}O$	220	Terbutaline	$C_{12}H_{19}NO_3$	225
Benzyl β-D-glucopyranoside	$C_{13}H_{18}O_6$	270	3,4-dihydroxymandelic acid	$C_8H_8O_5$	181
Benzohydroquinine	$C_{10}H_8O_2$	160	Dehydroabietic acid	$C_{20}H_{28}O_2$	300
Hydroxyamphetamine	$C_9H_{13}NO$	151	Diazoprogesterone	$C_{21}H_{30}N_4$	338

disease (Heneka *et al*., 2010). Norepinephrine is synthesized from tyrosine as a precursor and packed into synaptic vesicles. It performs its action by being released into the synaptic cleft, where it acts on adrenergic receptors, followed by the signal termination, either by degradation of nor -epinephrine or by uptake by surrounding cells., this reference support the role of nor-epinephrine compound as anti-inflammatory agent (Heneka *et al*., 2010).

The present results indicate the efficacy of methanolic extract and alkaloid fraction, as anti-inflammatory agent, so the analysis of methanolic extract and alkaloid fraction are important for determining the active compounds which may be responsible for these activity.

Antioxidant activity: The antioxidant activity of extracts of *Launeae* and *Santolina*, were tested its scavenging activities on DPPH radicals. DPPH test 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, that can be quantitatively measured from the changes in absorbance. The ratio of antioxidant/DPPH required to decrease the concentration of DPPH to 50% of its initial value, denoted as EC_{50} (Efficient Concentration), is an indicator of antiradical activity, i.e., the lower the EC50, the more potent the scavenging activity (Kummer, 2010). DPPH radical scavenging activity of various leaf extracts of Launaea and Santolina were denoted in Table 2. All the extracts showed different levels of DPPH radical scavenging activity over the range of 2-10 mg/ml concentration and the EC50 values of MeOH extracts and alkaloid fraction of Launaea and Santolina were 27.85, 30.55 25.94 and 32.22 mg/ml, respectively. The scavenging activity of extract (50%) was less than that of ascorbic acid (96%).

Alkaloid fraction exhibited strongest DPPH radical scavenging activity compared to other methanolic extracts. Standards and all the extracts showed a dose dependent inhibition on the DPPH radicals (Table 2).

GC-MS-analysis: GC-MS method used for the analysis of the obtained extracts can be an interesting tool for testing the amount of some active principles in herbs used in cosmetic, drugs, pharmaceutical or food industry. The acidic fractions were silylated and subjected to GC-MS investigation. It is evident from the

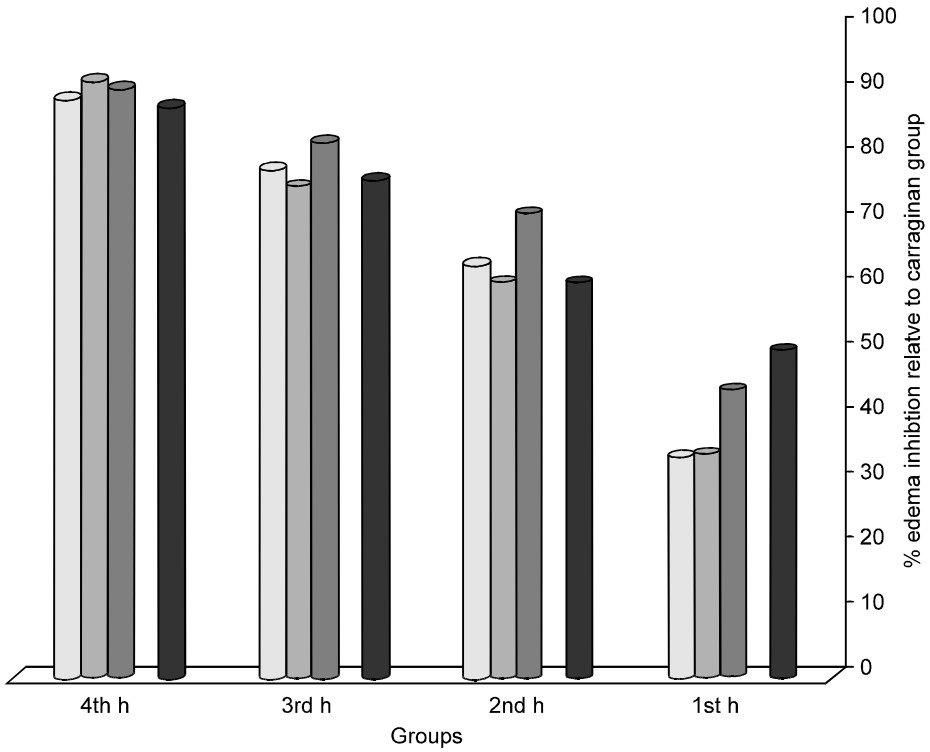

Fig. 1: Anti-oedema effect of different extracts (200 mg/kg)

Table 3 that all fractions have a complex chemical composition. Some of the GC-MS peaks remained unidentified, because of lack of authentic samples and library data of corresponding compounds.

All the compounds have been identified for the first time in *Launaea* and Santolina, Further chromatographic fractionation of the crude alkaloidal fraction (CAF) led to the isolation 5 fraction. The analysis of alkaloid fraction of the plant launaea showed 12 constituents, the major constituents, floroatropine, Kopsinyl alcohol, DL-Norepinephrine and Terbutaline. identification of complex mixtures of alkaloids by GC-MS are important method (Ionkova *et al*., 1994).

Non alkaloid fraction of Launaea analysis by GC-MS revealed the presence of important phytochemical constituents, Tetrahydroarucarolone, Menbutone, Diazoprogesterone and Dehydroabietic. The analysis of alkaloid fraction of Santolina revealed the presence of Hydroxyamphetamine, while nonalkaloid give more compounds most of them are diterpene AS (Table 3). Thus GC-MS analysis is the first step towards understanding the nature of active principles in this medicinal plant. However, isolation of individual phytochemical constituents may proceed to find a novel drug.

Discussion: Standard alkaloid extraction procedures carried out on the samples gave residues that tested positive for alkaloids (orange colour) with the Dragendorff reagent. The alkaloid yield was approximately 1.8% in both samples.

The analysis of plant *Launaea mucronata* by GC-MS revealed the presence of some compound belong to neurotransmitters catecholamines (norepinephrine and epinephrine), these compounds have important role in plant and animal.

In plants, neurotransmitters demonstrate a high biological activity, playing a role as chemosignals, regulators of membrane permeability, growth and development regulators, etc. (Roshchina, 1991, 2001; Szopa *et al*., 2001). A defense function for catecholamines in the plant cell has also been considered in the literature (Kulma and Szopa, 2007). Increased dopamine content in some algae, in particular *Ulvaria obscura*, has led to the consideration of the neurotransmitter as a feeding deterrent (van Alstyne *et al*., 2006). This is a novel ecological role for a catecholamine. The confirmation of dopamine production acting as defense mechanism against grazers was done from experiments with isopods, snails and sea urchin eating the agar-based foods contained exogenous dopamine (Nelson *et al*., 2003).

Stress stimulates the formation and releasing of biogenic amines, in particular epinephrine, a hormone produced during stress that affects heart rate, blood circulation and other functions of the body.

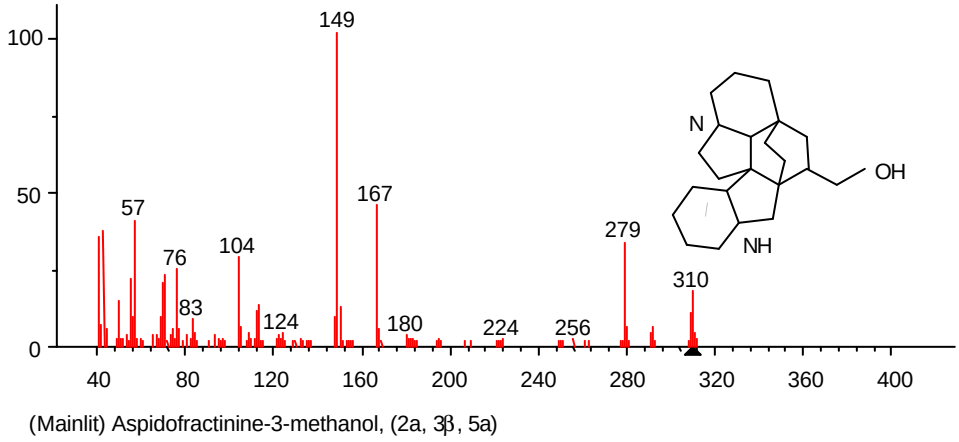

Fig. 2: Mass spectroscopy of compound Aspidofractinine-3-methanol

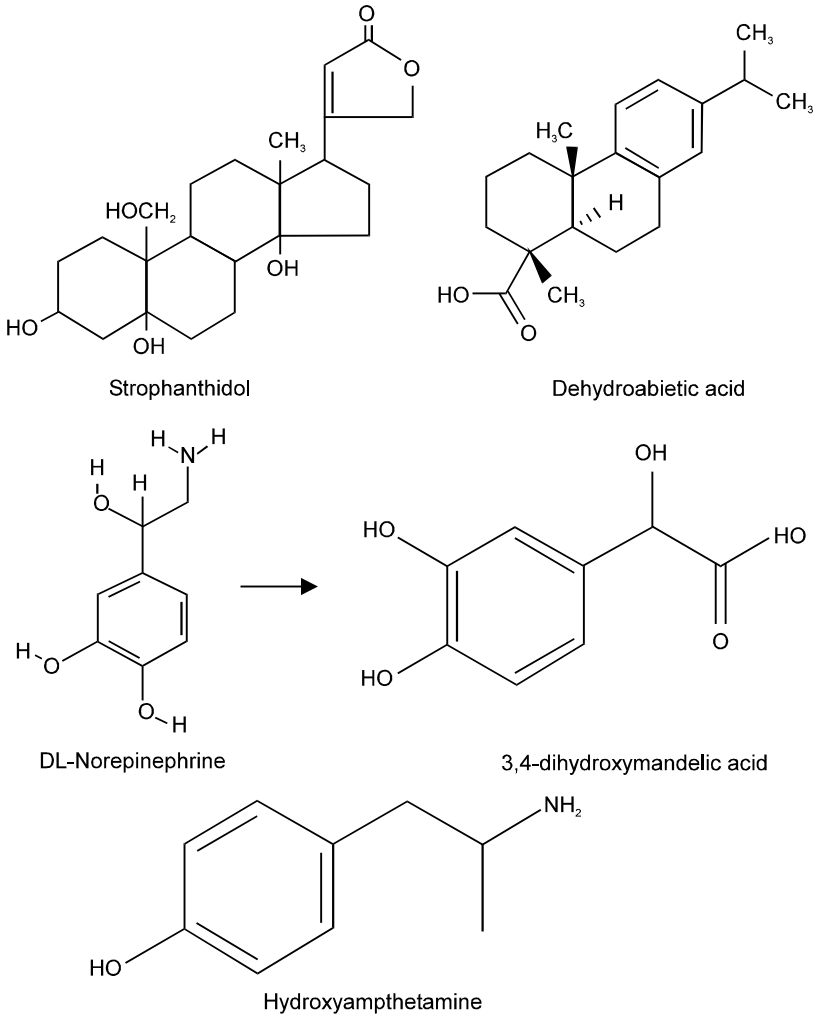

Fig. 3: Compound structures identified by GC-MS

Microorganisms possess the ability to recognize hormones within the host and utilize them to adapt to their surroundings. Norepinephrine and epinephrine, which are released during human stress responses,

may act as environmental cues to alter the growth of individual microbes (Roshchina, 2001).

Catecholamines have also been found in many plants and their synthesis is regulated by stress conditions. Their role and actions are only partly understood. They are involved in many aspects of growth and development. They affect the actions of various plant hormones and regulate carbohydrate metabolism. They serve as the precursors of isochinolic alkaloids and melanin. Catecholamines protect plants against pathogens and are involved in nitrogen detoxification. (Kulma and Szopa, 2007). This support the antioxidant activity of alkaloid fraction of the plant.

Examination of the compounds known as neurotransmitters or biomediators reveals a similarity in their main functions at the cellular level for all living organisms. These compounds change the membrane ion permeability, electrical characteristics of the cells and in final we see the integral response of the cell or organism as a whole-stimulation or inhibition of growth and development. Neurotransmitters regulate their own metabolic processes within a cell and the relationships (allelopathy) between neighbors with biogenesis, may serve as attractants or repellents as well as oxidative agents (biogenic amines).

The analysis of alkaloid fraction of *Launaea mucronata* shows the presence of norepinephrine, floroatropine, Kopsinyl alcohol and epinephrine, also the alkaloid fraction give high anti-inflammatory inhibition than methanolic extract, this confirm the role of these compounds as in anti-inflammatory agent by Carrageenin method.

Conclusion: In conclusion, the present study revealed that extracts of two plants *Launaea* and *Santolina* contains pharmacologically active substances effective for management of anti-inflammatory and antioxidant. This study also scientifically justifies the traditional claim of usefulness of these plants against anti-inflammatory. Further investigation is necessary for isolation, identification and characterization of different active compounds from the extract and for elucidating their mode of action, responsible for these properties on different biological systems. Other important something, the detection of compound 3,4-dihydroxymandelic acid and DL-Norepinephrine in the same fraction, support the structure, where compound dihydroxymandelic, formed from the enzymatic degradation of DL-Norepinephrine.

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