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PHYTOCHEMICAL, ETHNOPHARMACOLOGICAL, AND POTENTIAL THERAPEUTIC USES OF THE GENUS *FELICIA*

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ABSTRACT

Family *Asteraceae* is considered one of the largest medicinally important families which includes valuable members economically and therapeutically. Secondary metabolites mainly flavonoids, sesquiterpene lactones, triterpenoids besides volatile oils are among the active principles reported in this family. Concerning the genus *Felicia*, no enough data is available in literature about it's phytoconstituents, in spite of its common traditional use in several areas of the world especially South Africa. The aim of the review is to provide collective and updated information about this genus including its taxonomy, description, active principles, ethno-pharmacology and pharmacological uses. We mainly aim to encourage researchers to discover this genus, particularly those species whose phytoconstituents and biological activities have not been explored until now.

KEYWORDS

Asteraceae, *Felicia*, Acetylenic compounds, Isocoumarins, Essential oils, Terpenes, Ethno-pharmacology, Anti-inflammatory and Antioxidant.

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INTRODUCTION

Plants are valuable sources of medicine. Investigation on natural products aims to determine medicinal values of plants by the exploration of existing scientific knowledge, traditional uses to discover potential pharmacologically active agents. Many researchers use phytochemicals as template to discover safe and effective drugs (Balunas and Kinghorn, 2005)[1].

The *Asteraceae* is considered one of the widespread families of flowering plants include about 1000-2000 genera and 23,000 species (Tariq, 1987)[2]. This

family is represented in numerous environments from sea level to mountain tops all over the world. More than 12 % of the plants mentioned in the Saudi Arabia flora belong to the *Asteraceae* family (Migahid, 1978)[3]. *Asteraceae* is presented in Egypt by 97 genera including 230 species (Zareh, 2005)[4]. This family contains different classes of phytoconsitutents as flavonoids, sesquiterpenes, triterpernoids, coumarins and volatile oil. Plants belonging to this family show a vast range of biological activities including cytotoxic, anticancer activities (Jimenez-Usuga *et al,* 2016)[5] anti-inflammatory, anti nociceptive and antipyretic activities (Ashafa, 2010b)[6], hypoglycemic action (Nagwa Ammar, *et al*, 1993)[7], antiviral against herpes simplex virus (Binns *et al,* 2002)[8] and selective Cox 2 inhibition activities (Janmejai *et al,* 2009)[9]. These Plants are also considered important sources of chemo-preventive agents due to their content of different classes of antioxidant compounds as flavonoids and triterpenoids (Bruce *et al*, 2013)[10].

Felicia is a genus of small shrubs, annual or perennial herbaceous plants, with 85 known species. Like in almost all members of *Asteraceae*, leaves are alternate and linear or oblanceolate (Oritz, 2007)[11]. The individual flowers are pentamerous, small and clustered in typical heads, surrounded by an involucre; there are two or four whorls of bracts. Capitulum is solitary, heterogamous and radiate. The disc florets of capitulum are colored yellow, seldom white or bluish black, while ray florets one single whorl are colored purple but sometimes are blue, pink, white or yellow and rarely ligulate florets are absent. According to Nesom (1994)[12] this genus is characterized by obovate and flat cypselas with two thickened lateral ribs and pappus with a single series of generally caducous bristles.

Taxonomy: (Beentje, 1999)[13]

Kingdom : Plantae
Phylum : *Tracheophta*
Class : *Magnoliopsida*
Order : *Asterales*
Family : *Asteraceae*
Subfamily: *Asteroideae*
Genus : *Felicia*

Genus *Felicia* includes many species as

F. abyssinica, F. aculeate, F. alba, F. amelloides, F. cana, F. diffusa, F. dubia, F. erigeroides, F. filifolia, Felicia hirta, F. hispida, F. muricata, F. martinsiana , F.merxmuelleri, F. minima, F. ovata, F. petiolata, F. rosulata, F. uliginosa, F. wrightii and *etc.*

Phytochemistry of genus *Felicia*

Previous researches showed that plants from genus *Felicia* include various constituents as essential oil, esters, acetylenic compounds , isocoumarins and terpenes Phytochemical screening of *Felicia erigeroides* extract indicated that leaves extract contained flavonoids, saponins and tannins, stem extract contained flavonoids and triterpene steroids, while root extract contained saponins (Salie *et al*, 1996)[14].

Essential oils

The essential oil of *F. muricata* leaves was extracted by hydro distillation, analyzed by GC/MS, 38 compounds of the essential oil constituting 97.5% of the total oil composition were identified.

The oil was dominated by monoterpenoid hydrocarbons and contained small amount of monoterpinoids alcohols and phenols besides sesquiterpenoid hydrocarbons and alcohol.

Limonene constituted the major monoterpenoid hydrocarbon (26.5%), followed by myrcene (18.7%), α-Pinene (9.1%), *trans*-ocimene (4.8%), β-pinene (3.5%), 1, 3, 8 *para*- menthatriene (2.7%) and *cis*-ocimene (2.2%). The monoterpenoid alcohols were represented by α-terpineol (3.4%), terpinen-4-ol (0.4%), linalool (0.5%) and borneol (0.3%). Methyleugenol (0.4%) and eugenol (0.1%) represented the main phenolic compounds of the oil.

The sesquiterpene hydrocarbons were represented by *trans*-farnesene (1.7%), germacrene D (0.4%) and bicyclogermacrene (0.4%), while farnesol (0.1%) represented the sesquiterpenoid alcohols. (Ashafa *et al,* 2008)[15]. The oil was characterized by the presence of the non-terpenoid polyacetylenic compound, *cis*-lachnophyllum ester (16.2%) (1). the

high percentage of lachnophyllum ester in the essential oil is characteristic of family *Astreaceae* (Avato and Tava 1995[16], Hrutfiord *et al,* 1988)[17]. Figure No.1.

Esters

Isoeugenol isovalerate (2) was isolated from both aerial parts and roots of *Felicia wrightii*. Eugenol isovalerate (3) was isolated from the aerial parts of *Felicia wrightii*. The olefinic ester Tetradeca 5, 7, 9, 11 tetraenoic acid methyl ester (4) was isolated from the aerial parts of *F.uliginosa*. Figure No.2.

Isocoumarins

3-propyl-isocoumarin (5) was isolated from the roots of *Felicia wrightii*. Figure No.3.

Acetylenic compounds

(2*Z*, 8*Z*) Matricaria methyl ester(6) was found in *F.ulignosa* root extract (Bohlmann, *et al,* 1976)[18], (2*E*, 8*Z*) Matricaria methyl ester (7) was obtained from *F.filifolia* roots (Bohlmann, *et al,* 1979)[19], deca -2*E*, 8*E*-dien-4, 6diyne-1, 10-diyldiactate (8), deca -2*E*, 8*Z*-dien-4, 6 diyne-1, 10- diol (9), 10-hydoxy-deca-2*E*, 8*Z*-dien-4, 6-diyn-1-yl acetate (10), deca-2*Z*, 8*Z*-dien-4, 6-diyne-1, 1-diol (11), 2-[6-hydroxy-hex-4c-en-2-in-1yl*]* (12) and 2-[6-hydroxy-hex-4c-en-2-inyliden]-2, 5-dihydrofuran (13) were obtained from the aerial parts of *F.filifolia*. Figure No.4.

Compound (12) is suggested to be acyclization product of compound (11) Compounds (12 and 13) are isomers (Bohlmann, *et al,* 1979)[19]. Figure No.5.

Terpenes

Terpenes are one of the most diverse classes of plant secondary metabolites, have important role in fragrance, taste and bioactivity of many plants. Plants of genus *Felicia* were reported to be rich in terpenes.

Sesquiterpenes

Germacrene D (14) was isolated from the aerial parts of *Felicia erigeroides* (Bohlmann, *et al,* 1979)[19]. Farnesene (16) and Bicyclogermacrene (17) were isolated from the aerial parts of *F.filifolia***.**

Diterpenes

Neophytadiene (15) was isolated from aerial parts of *Felicia erigeroides* (Bohlmann, *et al,* 1979)[19]. Figure No.6.

Ethno pharmacology

Some members of genus *Felicia* are used in folk medicine of South Africa. The Zulu, Sotho and Xhosa traditional healers used the aqueous extract of *Felicia muricata* leaves as an oral remedy for pains, fever, inflammation, haeadache as well as stomach diseases and catarrh (Hutchings .A and Van Staten, 1994)[20].

According to Hutchings *et al,* 1996[21] and Pooley 1998[22], hot leaves infusions of *Felicia erigeroides DC* were administered as enemas for intestinal parasites, abdominal pains and also as purgatives.

Pharmacological activity

The aqueous extracts from several plants of genus *Felicia* were found to have strong antipyretic, anti nociceptive and anti-inflammatory activities in animal models (Ashafa *et al*, 2010b)[6]. Further studies are needed to identify the secondary metabolites responsible for their biological activities.

Anti-inflammatory activity

The aqueous extract *of Felicia muricata* leaves was tested for its anti-inflammatory activity by rat paw edema test using carrageen an and egg albumin to induce rat paw edema. Egg albumin-induced rat paw edema test doses of 100 and 200mg/kg body weight of the aqueous extract started the decrease of the paw edema volume by 30min after treatment. While, 50mg/kg body weight did not show this effect until after 2 hr of administration. The 200mg/kg body weight of the extract showed the most astounding rate of inhibition on the egg albumin-induced paw edema compared with orally 10mg/kg body weight of indomethacin that reduce egg albumin induced paw edema from 60 to120min after administration (Ashafa *et al,* 2010a)[23].

According to McGaw *et al,* (1997)[24], aqueous extract of *Felicia muricata* leaves showed 80 - 90% inhibitory activity against cyclooxygenase, an important enzyme in the prostaglandin biosynthesis pathway.

Cyclooxgenase enzyme inhibitory activity of petroleum ether, dichloromethane, ethanol and water extracts of *Felicia erigeroides* was examined using methods of Jager *et al*, (1996)[25] as modified

by Zschocke and Van Staden (2000)[26] and using Indomethacin as a reference drug with dose of 5µM for COX-1 and 200µM for COX-2 inhibition. Concentration of 250µg/ml for organic extracts and 2000µg /ml for water extracts were examined and COX inhibition of the extracts was calculated by comparing the amount of radioactivity present in the sample to that in the solvent blank. According to Aremu *et al,* (2010)[27], *Felicia erigeroides* dichloromethane leaves extract showed potent inhibitory activity of COX-1 followed by the petroleum ether fraction. *F.erigeroides* petroleum ether and dichloromethane stem extracts showed nearby equal potent inhibitory activity of COX-2. The aqueous extract of leaves and stem showed week activities on COX-1 inhibition and no activity on COX-2 inhibition.

Anti nociceptive activity

Felicia muricata leaves aqueous extract was tested for anti nociceptive activity using acetic acid-induced writhing test, formalin-induced pain and tail immersion method. Writhing test was carried out according to Gaertner *et al,* (1999)[28] procedure. Subcutaneous morphine sulfate (5mg/kg) was used as reference agent. Different doses of the extract (50, 100, 200mg/kg) were administered orally and reduced the number of writhes induced by acetic acid. The best result was obtained with conc. of 200mg/kg body weight that showed more anti nocieceptive activity more than morphine (Ashafa *et al*, 2010a)[23].

Antipyretic activity

The different doses (50, 100, 200mg/ kg body weight) of *Felicia muricata* leaves aqueous extract decreased the raised body temperature caused by brewer's yeast of the animals at various times of the test. The 200mg/kg body weight of the aqueous extract decrease of the raised body temperature after 1 h, While indomethacin (10mg/kg body weight) decrease the raised body temperature of the animal after 30 min after administration. (Ashafa *et al*, 2010a)[23].

Antioxidant activity

The effect of aqueous and organic extracts from the leaves of *Felicia muricata* thumb on DPPH radical was estimated using the method of Liyana-Pathiranan and Shahidi, 2005[29]. ABTS radical scavenging assay was conducted also for the same extract. *F.muricata* leaves extracts were effective scavengers of ABTS radical compared with standard antioxidant Butylated hydroxytoluene (BHT) 5mg/mL. The percentage inhibition for ABTS radical was 94.55%for aqueous extract, 99.21% for methanol extract, 98.66% for acetone extract, 97.27% for ethanol extract and 99.27% for ABTS.

The scavenging of ABTS by the extracts was found to be higher than that of DPPH. This indicates that the extract can scavenge different free radicals in different systems, indicating that they may be useful therapeutic agents for treating radical-related pathologic damage (Ashafa *et al,* 2010b)[6].

Antibacterial and antifungal activity

The minimum inhibitory concentration (MIC) values of *Felicia muricata* volatile oil were determined for different micro-organisms using the microplate dilution method. The result showed the essential oil inhibits many gram positive bacteria for example *Streptococcus aereus* and *Streptococcus faecalis* and gram negative bacteria for instance *klebsiella pneumonia*, *Escherichia coli* and more active than streptomycin for some bacteria as *Pseudomonas aeruginosa* strain. (Ashafa *et al,* 2008)[15].

The MIC values of *Felicia erigeroides* extracts against gram-positive bacteria as *Bacillus subtilis* and *Staphylococcus aureus*, and gram-negative bacteria as *Escherichia coli* and *Klebsiella pneumoniae* were determined using the micro plate technique. Neomycin (100µl, 0.4mg/ml) was used as standard anti-bacterial agent. Ethanolic extract of *Felicia erigeroides* leaves, dichloromethane and petroleum ether extracts of stem have a good antibacterial activity.

Minimum fungicidal concentration (MFC) and MIC values of *Felicia erigeroides* extracts against *Candida albicans* were determined using micro plate technique. Amphotricin B (100µl, 0.25mg/ml) was used as standard anti-fungal agent. All fractions have low antifungal activity against *Candida*

albicans. Extracts with MIC or MFC values less than 1.0mg/ml were considered to have a high antibacterial and antifungal activity (Aremu *et al*, 2010)[27].

Antiprolifertaive and cytotoxic activity

The methanolic extract of *Felicia dentata* aerial parts was examined for antiprolifertaive and cytotoxic activity using MTT assay in A2780 (ovarian carcinoma), MCF7 (breast carcinoma), HeLa (cervical carcinoma), RKO (colorectal carcinoma) and, Jurkat (leukemia) cell lines. The results showed that this extract had low activity in the MTT assay compared to Etoposide as reference drug (Bader *et al*, 2018)[30].

Anthelmintic activity

The effect of *F.erigeroides* leaves and stems extracts on the viability of the free living nematode larvae *Caenorhabditis elegans* (50µl contain 100 worms) was determined in *vitro* using colorimetric assay developed by James and Davey (2007)[31] and modified to determine minimum lethal concentration (MLC). MLC values of the petroleum ether, dichloromethane and ethanol extracts of *F.erigeroides* leaves and stems were determined using two-fold serial dilution. Levamisole 100µl of 1mg/ml was used as a reference drug. The best MLC values were exhibited by the dichloromethane leaves extract (520µg/ml) followed by petroleum ether leaves extract (1040µg/ml) then the stem dichloromethane extract (2080µg/ml), while MLC for the standard levamisole was 40µg/ml. Aqueous extract of both leaves and stems exhibited weak anthelmintic activities against *Caenorhabditis elegans* (Aremu *et al,* 2010)[27].

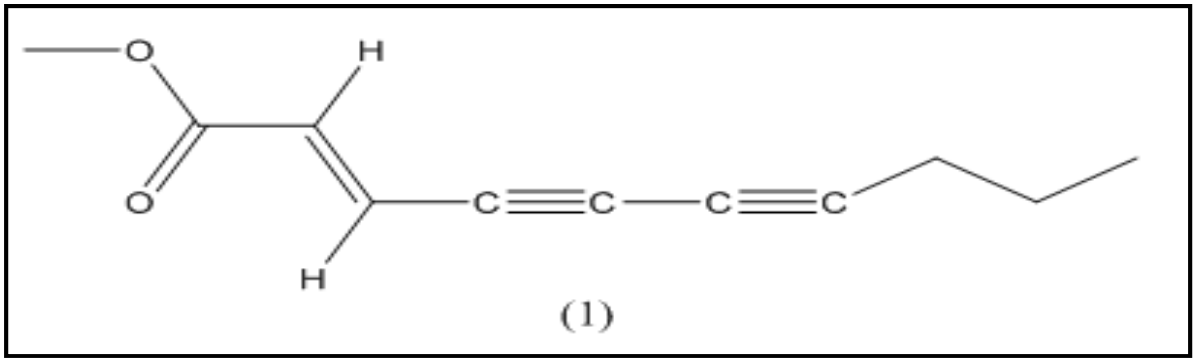

Figure No.1: *cis*-lachnophyllum ester isolated from essential oil of *F.muricata* leaves

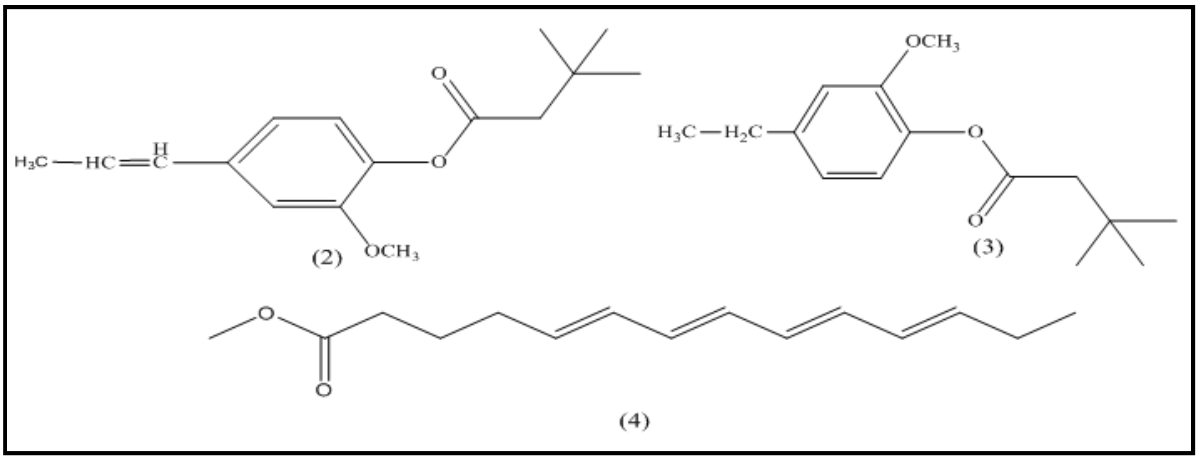

Figure No.2: Esters isolated from genus *Felicia*

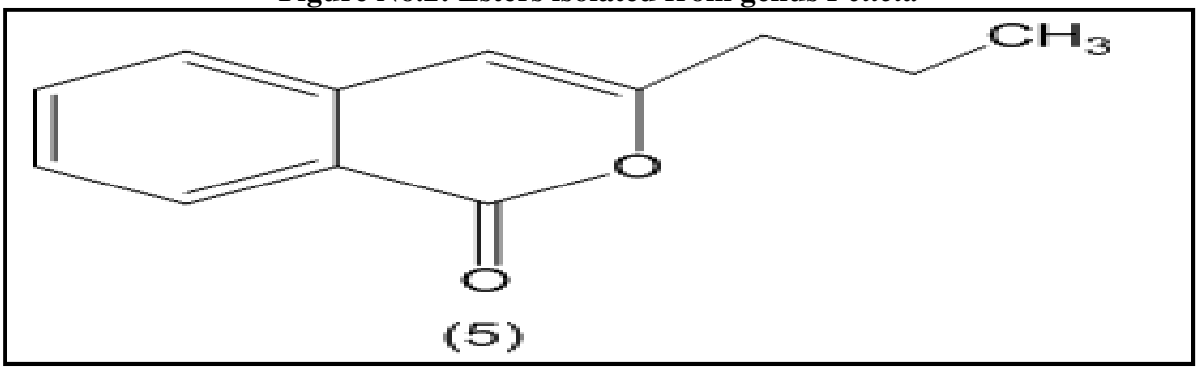

Figure No.3: Isocoumarin isolated from the roots of *Felicia wrightii*

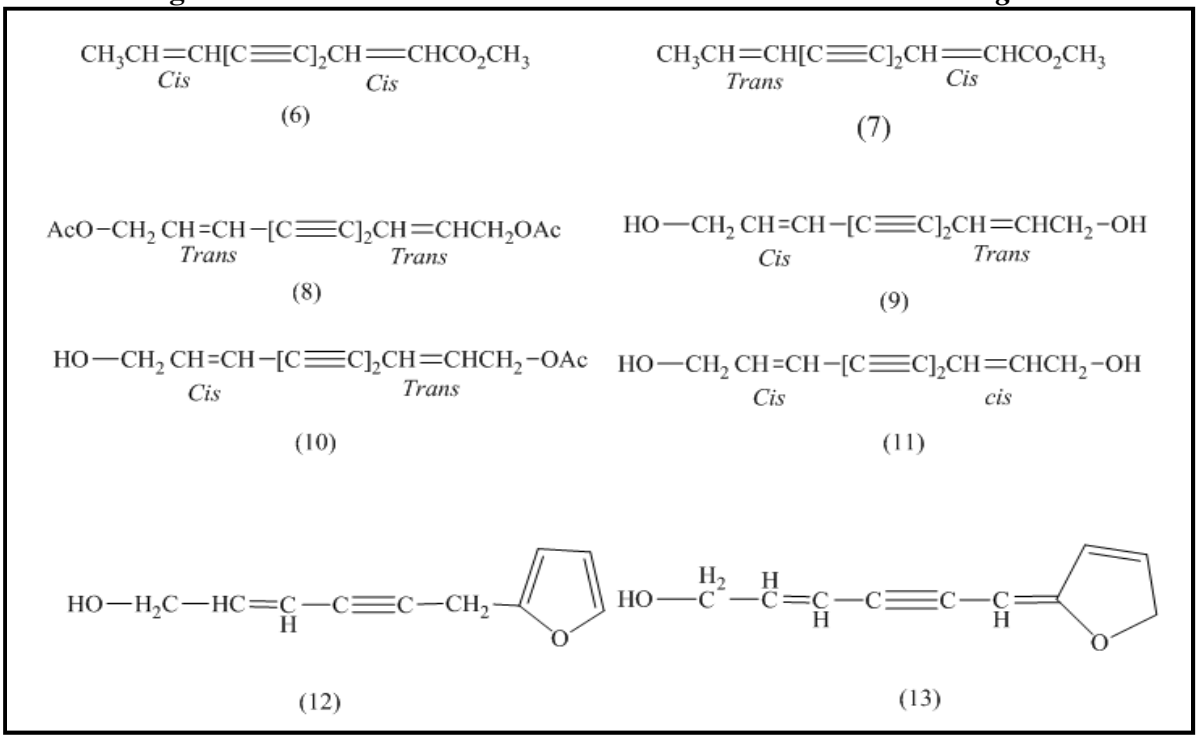

Figure No.4: Acetylenic compounds isolated from genus *Felicia*

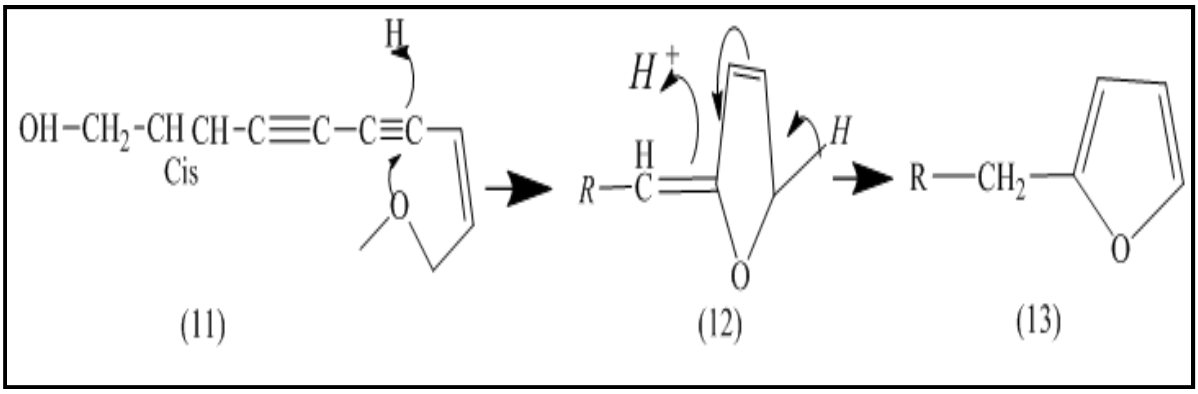

Figure No.5: Schematic presentation of possible Mechanism for conversion of compounds 10 and isomerization of compound 11

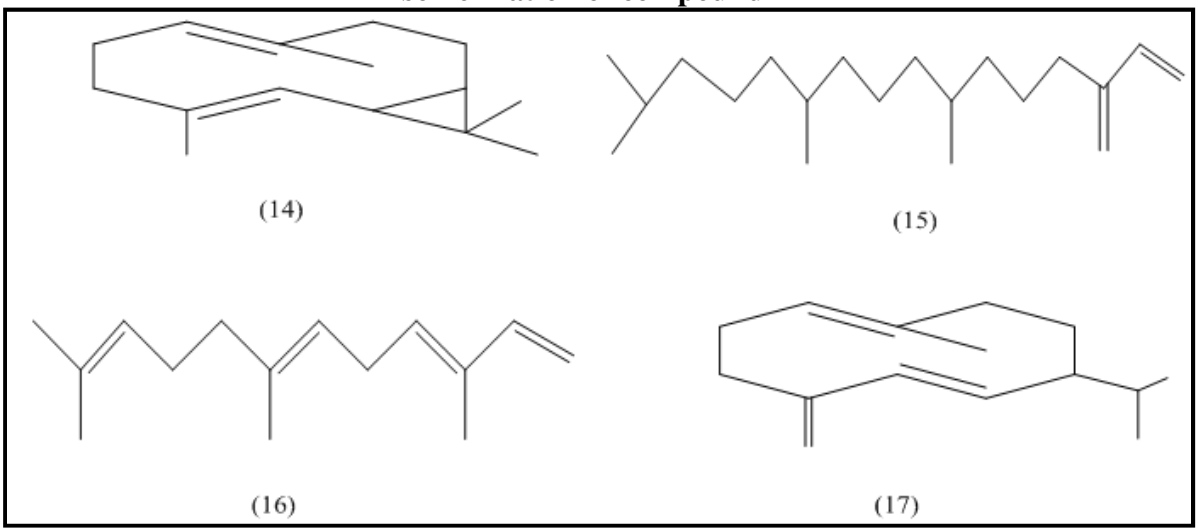

Figure No.6: Structures of major terpenes isolated from *Felicia* genus

CONCLUSION

Although there is rare data about chemistry and biology of genus *Felicia*, this review shed light on the available phytoconstituents and biological activities on the few studied species. The review revealed species contained different classes of phytoconsituents as essential oils, esters, acetylenic compounds, isoeugenol, iso-coumarin derivatives and terpenes. It also showed some biological activities of certain studied species as anti-inflammatory, anti-nocicptive, antipyretic, antioxidant, anthelmintic, antibacterial, antifungal and cytotoxicity. Hence, further research is needed to investigate and isolate other compounds from this genus and discover possible biological activities.

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CONFLICT OF INTEREST

There is no conflict of interest.

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