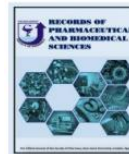




RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES



Biological Review on Different Species Belonging to *Zygophyllum* genus

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Abstract

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Nature has always been an infinite supply of biologically active substances. There are different natural sources for remedies discovery such as microorganisms, terrestrial plants, terrestrial invertebrates & vertebrates and sea macro and microorganisms. In drug discovery studies, medicinal plants have historically been recognized as a valuable source of bioactive compounds. Zygophyllaceae is a diverse family with 27 genera and 285 species including trees, shrubs and herbs. *Zygophyllum* species plants are common in salty and gypsophile regions and they are frequently used as medicines in folk medicine. They have been used for different diseases as gout, hypertension, diabetes, fungal infections and rheumatism. Therefore, a lot of phytochemical investigations were carried out to screen these genus plants and these studies revealed various chemical constituents belonging to different chemical classes as flavonoids, triterpenes, saponins, phenolics, sterols, esters and essential oils. This review will include the most significant previous biological studies of different species of the genus *Zygophyllum*.

Keywords: *Zygophyllum*, Antioxidant, Anti-diabetic.

1. Introduction:

Nature has always been an infinite supply of biologically active substances. There are different natural sources for remedies such as microorganisms, terrestrial plants and sea macro and microorganisms (Dar *et al.*, 2017). In drug discovery studies, medicinal plants have historically been recognized as a valuable source of bioactive compounds (Yaripour *et al.*, 2017). The WHO estimates that 80 percent of the world's population, primarily those living in developing nations, rely on plant derivative medications for their healthcare, which are typically replaced by pharmaceutical ingredients in the West. The most popular pharmaceuticals in the past few decades were discovered from natural chemical compounds as taxol from *T. brevifolia* & morphine from *Papaver somniferum* (Dar *et al.*, 2017). Zygophyllaceae is

a diverse family with 27 genera and 285 species including trees, shrubs and herbs (Hussein *et al.*, 2011). *Zygophyllum* species plants are common in salty and gypsophile regions and they are frequently used as medicines in folk medicine (Bourgou *et al.*, 2017). They have been used for different diseases as gout, hypertension, diabetes, fungal infections and rheumatism (Shawky *et al.*, 2019). Therefore, a lot of phytochemical investigations were carried out to screen these genus plants and these studies revealed various chemical constituents belonging to different chemical classes as flavonoids, triterpenes, saponins, phenolics, esters and essential oils (Hussein *et al.*, 2011; Bourgou *et al.*, 2017; Shawky *et al.*, 2019). This review will include the most significant previous biological studies of different species of the genus *Zygophyllum*.

Table 1: Biological activities reported in genus *Zygophyllum*

I. Antioxidant activity			
Active Compounds / extracts	Details	Species	Reference
Aq. And ethanol extracts	2, 2 diphenyl-1-picrylhydrazyl (DPPH) assay	<i>Z. album</i>	(Aboul-Enein <i>et al.</i> , 2012)
Essential oil leaves extract (diethyl ether).	Dichloromethane and ethanol extracts were endowed with a powerful anti-acetylcholinesterase activity with IC ₅₀ values of 40 and 58 µg/mL, respectively. These two extracts exhibited the highest DPPH radical scavenging activity (IC ₅₀ =0.2 mg/mL), the highest total anti-oxidant capacity (185.2 and 222.4 mg vitamin E/mg extract, respectively)	<i>Z. album</i>	(Kchaou, <i>et al.</i> , 2018)
Hexane, dichloromethane and methanol extracts	Tunisian <i>Z. album</i> shoots <i>in vitro</i> using the ORAC assay, as well as, <i>in-vivo</i> using a cellular based-assay using DCFH-DH, a useful indicator of reactive oxygen species (ROS). The most polar extract (methanol) had a strong antioxidant ORAC capacity (1.19 ± 0.07 µmol Trolox/mg) and the dichloromethane extract proved the most antioxidant activity in cell (WS1) based-assay (IC ₅₀ = 57 µg/ml).	<i>Z. album</i>	(Bourgou <i>et al.</i> , 2017)
Aqueous extract	Aqueous extract of aerial parts of <i>Z. album</i> showed antioxidant activity using DPPH scavenging assay.	<i>Z. album</i>	(Ouffai <i>et al.</i> , 2022)
Butanol fraction	The antioxidant activity was measured using DPPH (2, 2'-diphenyl-1-picrylhydrazyl) test. Butanol fraction exhibited the	<i>Z. cocconiem</i>	(El-Shora <i>et al.</i> , 2016)

	highest scavenging activity		
Water fraction & chloroform fraction	The antioxidant activities were investigated by DPPH test, ferric reducing activity and phosphomolybdenum assay. The best DPPH scavenging activity was found in water fraction followed by chloroform fraction (IC ₅₀ = 25 and 38.5 µg/ml, respectively).	<i>Z. cornutum</i>	(Belguidoum <i>et al.</i> , 2015)
Methanol & Ethyl acetate extracts of aerial parts	The methanol extract revealed weak antioxidant activity while the ethyl acetate extract showed strong activity in these antioxidants radical -scavenging activities (DPPH) tests.	<i>Z. eichwaldii</i>	(Mazoochi <i>et al.</i> , 2021)
Methanolic extract	Methanolic extracts of leaves, flowers and roots were evaluated using 2, 2-diphenyl-1-picrylhydrazyl (DPPH) method. The extracts of leaves and flowers of <i>Z. fabago</i> showed the remarkable results in free radical-scavenging activity.	<i>Z. Fabago</i>	(Yaripour <i>et al.</i> , 2017)
Ethanol and methanolic extracts	These extracts showed noticeable DPPH radical-scavenging activity as compared to ascorbic acid.	<i>Z. hamiense</i>	(Shehab <i>et al.</i> , 2015)
Shoot extract	DCFH-DH, a useful indicator of reactive oxygen species (ROS)	<i>Z. simplex</i>	(Bourgou <i>et al.</i> , 2017)
II. Anti-diabetic activity			
Aqueous and ethanol extracts	<i>Z. album</i> extracts prevents the diabetic induced MDA levels via the enhancement of the tissue glutathione reductase (GSH), blood vitamin C levels, superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx).	<i>Z. album</i>	(Bourgou <i>et al.</i> , 2017)
Essential oil of <i>Z. album</i> leaves	The IC ₅₀ value of essential oil of <i>Z. album</i> against α - amylase was 43.17 µg mL and that against pancreatic lipase was 85.95 µg mL, suggesting powerful anti-diabetic and anti-obesity effects.	<i>Z. album</i>	(Kchaou, <i>et al.</i> , 2018)
Hexane, ethyl acetate, and butanol extracts	The pancreatic α -amylase inhibitory activities increased in the order of Hexane fraction < Butanol fraction < Ethanol extract.	<i>Z. album</i>	(Mnafgui, <i>et al.</i> , 2014)
Ethanol extract	The antihyperglycemic effect of ethanol extract of the whole plant of <i>Z. album</i> was investigated on blood glucose, serum lipids and	<i>Z. album</i>	(Ghoul, <i>et al.</i> , 2013)

	hepatic glycogen. After administration of the ethanolic extract, the increased level of plasma insulin is not significant in diabetic mice.		
The essential oil fraction	The oil was obtained by hydrodistillation and analyzed by GC-MS. It significantly decreased the activity of α -amylase in pancreas and serum of the diabetic rats by 43% and 38%, respectively, which led to reduce the serum glucose level by 60%.	<i>Z. album</i>	(Mnafgui, <i>et al.</i> , 2016)
Methanolic extract	The study suggests that <i>Z. cornutum</i> may provide a useful therapeutic option in the reversal of metabolic disturbances and oxidative stress-induced cardiac dysfunction in diabetes mellitus.	<i>Z. cornutum</i>	(Boumaza, <i>et al.</i> , 2016)
Aqueous aerial extract	In streptozotocin induced-diabetic rats, treatment with <i>Zygophyllum gaetulum</i> extract reduces glycemia, serum lipids and stimulates PON1 and LCAT activities. In addition, it reduces oxidative stress in the liver and kidney by decreasing TBARS levels and increasing antioxidant enzyme activities.	<i>Z. gaetulum</i>	(Guenzet, <i>et al.</i> , 2014)
Ethanolic extract	The ethanolic extract at 1 g/kg is endowed with a remarkable antidiabetic activity.	<i>Z. geslini</i>	(Medjdoub, <i>et al.</i> , 2012)
III. Anti-hyper-cholesterolemic			
Aqueous and ethanol extracts	Aqueous and ethanol extracts of <i>Z. album</i> from Tunisia exerts anti-diabetic and anti-hyper-cholesterolemic activities. Oral administration of the extracts reduced the blood glucose, total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) levels.	<i>Z. album</i>	(Bourgou <i>et al.</i> , 2017)
Ethanol extract	Administration of the ethanolic extract from plant (100 and 300 mg/kg body weight) for 14 days resulted in significant reduction in plasma glucose, cholesterol, triglycerides, low-density lipoprotein, very-low-density lipoprotein, hepatic glucokinase and glycogen in STZ diabetic mice.	<i>Z. album</i>	(Ghoul, <i>et al.</i> , 2013)
IV. Anti-obesity activity (Weight lowering)			
Ethanol extract	The study showed that ethanol extract can delay the occurrence of dislipidemia and hypertension.	<i>Z. album</i>	(Mnafgui, <i>et al.</i> , 2012)

V. Anti-atherogenic			
Methanol extract Of arial parts	The bioactive compounds in <i>Z. album</i> methanolic extract modulated most of inflammatory markers, prevented accumulation of lipid and lipoprotein biomarkers, regulated the major receptor regulators of hepatic cholesterol metabolism, as well as normalize lipid distribution in liver and aorta tissue.	<i>Z. album</i>	(Mnafgui, <i>et al.</i> , 2012)
VI. Anti-acetylcholinesterase			
Dichloromethane & ethanol extracts	Extracts were endowed with a powerful anti-acetylcholinesterase activity with IC ₅₀ values of 40 and 58 µg/mL, respectively.	<i>Z. album</i>	(Mnafgui, <i>et al.</i> , 2012)
VII. Anti-inflammatory			
Essential oil	The oil was obtained by hydro distillation and analyzed by GC-MS (ZAO). Male rats were divided into four groups: control, diabetic-untreated group, diabetic-treated group with acarbose (10 mg/kg), and diabetic-treated rats with OZA (200 mg/kg) for 30 d. At the end of the experimental period, the OZA significantly decreased the activity of α-amylase in pancreas and serum of the diabetic rats by 43% and 38%, respectively, which led to reduce the serum glucose level by 60% and lower of glycated hemoglobin (HbA1c) rate by 17% as compared with untreated diabetic animals. Moreover, the OZA treatment attenuated symptoms of diarrhea, improved lipid disorders, and hypertension through inhibiting the pancreatic lipase and angiotensin-converting enzyme (ACE) activities by 47% and 25%, respectively, in serum of diabetic rats.	<i>Z. album</i>	(Mnafgui, <i>et al.</i> , 2016)
Aqueous and ethanol extracts	<i>Z. album</i> extracts prevents the diabetic induced MDA levels via the enhancement of the tissue glutathione reductase (GSH), blood vitamin C levels, superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx).	<i>Z. album</i>	(Bourgou <i>et al.</i> , 2017)

Ethanol extract	70% ethanol extract of <i>Zygopgyllum macropodum</i> aerial parts (ZME) possessed analgesic and anti-inflammatory activities which related to inhibit the production of protein, PGE2 and TNF- α . The LD ₅₀ of ZME treated orally to mice was greater than 2000 mg/kg.	<i>Z. macropodum</i>	(Yang <i>et al.</i> , 2018)
Ethylacetate extract	Anti-inflammatory activity was assessed by carrageenan induced rat paw oedema in rats. Significant anti-inflammatory activity was observed at a dose of 100, 200 and 400 mg/kg body weight.	<i>Z. simplex</i>	(Kakrani <i>et al.</i> , 2011)
VIII. Anti-hypertensive			
Essential oil of leaves	The oil was obtained by hydro-distillation and analyzed by GC-MS. Males rats were divided into four groups: control, diabetic-untreated group, diabetic-treated group with acarbose (10 mg/kg), and diabetic-treated rats with Oil of <i>Z. album</i> (200 mg/kg) for 30 d. <i>Z. album</i> Oil treatment improved hypertension by inhibiting the pancreatic lipase and angiotensin-converting enzyme (ACE) activities by 47% and 25%, respectively, in serum of diabetic rats.	<i>Z. album</i>	(Mnafgui <i>et al.</i> , 2016)
Aqueous extract of whole plant	The extract dose-dependently reduced Blood Pressure and heart rate in normotensive and spontaneously hypertensive rats (SHRs). <i>In vitro</i> , the extract had no effect on basal perfusion pressure of the mesenteric vascular bed. When the perfusion pressure was raised with noradrenaline or potassium chloride, the extract produced a dose-dependent reduction in perfusion pressure.	<i>Z. coccineum</i>	(Gibbons <i>et al.</i> , 2001)
IX. Antimicrobial and antifungal			
Ethyl acetate extract	Ethyl acetate extract was potent antimicrobial effect on bacterial and fungal test organisms against <i>P. aeruginosa</i> with inhibition zone 20 mm and <i>F. moniliforme</i> with inhibition zone 22 mm	<i>Z. coccineum</i>	(El Badry <i>et al.</i> , 2015)

Ethanol extract	Ethanol extract showed antimicrobial activity against <i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i> & <i>Klebsiella pneumoniae</i> .	<i>Z. coccineum</i>	(Khafagi <i>et al.</i> , 2000)
Petroleum ether extracts from leaves & seeds.	Petroleum ether extracts from leaves & seeds of <i>Z. fabago</i> showed antimicrobial activity against several micro-organisms including gram negative bacteria (<i>Pseudomonas aeruginosa</i> & <i>Escherichia coli</i>), gram positive bacteria (<i>Staphylococcus aureus</i> & <i>Bacillus subtilis</i>), in addition to yeast (<i>Candida albicans</i>).	<i>Z. fabago</i>	(AL-Qaissi <i>et al.</i> , 2017)
Methanolic extract	The antifungal activity of synthesized nanoparticles, methanolic extract of <i>Zygophyllum qatarense</i> and silver nitrate were investigated against <i>Aspergillus niger</i> and <i>Penicillium digitatum</i> by disk diffusion and micro broth dilution methods. All the treatments showed antifungal activity, but silver nanoparticles when compared with other treatments had a significant effect against the <i>Aspergillus niger</i> and <i>Penicillium digitatum</i> .	<i>Z. qatarense</i>	(Barzegar <i>et al.</i> , 2018)
Methanolic extract	Methanolic extract of <i>Z. simplex</i> was examined for its antimicrobial potential against seven standard bacteria (<i>Proteus vulgaris</i> NCTC 8196, <i>Escherichia coli</i> ATCC 25922, <i>Bacillus cereus</i> NCTC 8236, <i>Salmonella typhi</i> NCTC 0650, <i>Klebsiella pneumonia</i> ATCC 53651, <i>Pseudomonas aeruginosa</i> ATCC 27853 and <i>Staphylococcus aureus</i> ATCC 25923) and one standard fungus (<i>Candida albicans</i> ATCC 7596). The extract showed antimicrobial activity against them.	<i>Z. simplex</i>	(Abdallah <i>et al.</i> , 2013)
X. Cytotoxic activity			
Methanol, ethyl acetate and water fractions obtained from shoot crude extract.	The cytotoxicity of each extract was assessed against Human colon carcinoma (DLD-1) and lung carcinoma (A-549) cell lines, as well as health skin fibroblast cell line (WS1). Result showed that among the three shoot fractions, the dichloromethane extract was significantly active against the two carcinoma cells (A-549 and DLD-1), with important IC ₅₀ values, respectively of 37 and 48 µg/ml. In fact, <i>Z. album</i> had an influence on tumour cell viability and targeted colon and lung carcinoma cell lines which could be attributed to the powerful cytotoxic compounds in	<i>Z. album</i>	(Bourgou <i>et al.</i> , 2017)

	dichloromethane fraction mainly triterpenes saponins and sterols.		
Aqueous-ethanolic extract	The <i>Z.cocconiem</i> extract revealed cytotoxic effects with IC ₅₀ values at 3.47, 3.19, and 2.27 µg/mL against MCF-7, HCT-116, and HepG2 cell-lines, respectively, in comparison to its standard referral inhibitor (staurosporine, IC ₅₀ , 135.33 ng/mL).	<i>Z. cocconiem</i>	(Mohammed <i>et al.</i> , 2021)
Ethyl acetate extract, Methanol extract and Acetone extract.	Cytotoxic effect of <i>Z. cocconium</i> extracts indicated that acetone extract showed maximum cytotoxic activity on HeLa cell line, whereas methanol extract showed maximum cytotoxic activity on MCF-7 cell line with cell line viability 13.36 and 35.19%, whereas the results of IC ₅₀ in HeLa cell line showed that the boiled water ethyl acetate extract had the most potent IC ₅₀ with 6.25 µg/ml.	<i>Z. cocconiem</i>	(El Badry <i>et al.</i> , 2015)
Aqueous and ethanol extracts	Anticancer activity of ethanolic and aqueous Egyptian <i>Z. simplex</i> extracts against Ehrlich Ascites Carcinoma Cells (EACC). The results displayed that the extracts gave anticancer activity more than 60% inhibition of proliferation.	<i>Z. simplex</i>	(Bourgou <i>et al.</i> , 2017)
XI. Urease inhibitor			
Five known compounds: Zygofaboside A, (3β,4α)- 3,23,30-trihydroxyurs-20-en-28-al 3,23-di(sulfate) sodium salt, Zygophyloside G, Zygophyloside E & 3β-O-[β-D-quinovopyranoside] quinovic acid 28-O-[β-D-glucopyranosyl] ester.	Five ursane type sulfated saponins have been isolated from the aerial parts of <i>Zygophyllum fabago</i> . The urease inhibitory effects of these compounds have been investigated for the first time as well as their molecular docking studies have also been carried out to check the structure–activity relationship. The molecular docking studies were performed only for the most active compound (Zygofaboside A).	<i>Z. fabago</i>	(Khan <i>et al.</i> , 2014)

XII. Cardioprotective effect			
Methanol extract of root extract	<i>Z.album</i> root extract had bioactive compounds that showed cardioprotective effects against deltamethrin-induced heart injury. The used extract showed improvement of heart injury markers as (ALT & LDH), protein oxidation and antioxidant capacity.	<i>Z.album</i>	(Feriani <i>et al.</i> , 2020)
Methanol extract of leaves extract	<i>Z.album</i> leaves extract showed cardioprotective effects. Chemical investigation of leaves extract showed fifteen saponins which have significant biological activity. These metabolites normalized the distribution of lipids in liver and aortic tissue and reduced the majority of inflammatory markers. They also avoided the buildup of lipid and lipoprotein biomarkers.	<i>Z.album</i>	(Feriani <i>et al.</i> , 2020)

3- Conclusion:

In this review we have discussed the biological activities reported in various species belonging to genus *Zygophyllum*. It is obvious that this genus is a rich source of compounds with wide range of biological activities.

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