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ANALGESIC EFFECTS of SCILLIROSIDE, PROSCILLARIDIN-A and TAXIFOLIN FROM SQUILL BULB *(Urginea maritima)* on PAINS

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The aim of the present study was to assess the clinical efficacy of proscillaridin-A ($C_{30}H_{42}O_8$), taxifolin ($C_{15}H_{12}O_7$) and scilliroside ($C_{32}H_{44}O_{12}$) and safety of squill bulb *(Urginea maritima)* (L.) Baker extract on various pains of spontaneous volunteer patients. In this study, 250 patients were monitored in coats. The average age of these patients were between 40 and 74 years old. Of these 100 were male and 150 female patients. Also, 60 % of proscillaridin-A ($C_{30}H_{42}O_8$), taxifolin ($C_{15}H_{12}O_7$) and scilliroside ($C_{32}H_{44}O_{12}$) solution in pure glycerin was applied as external on the pain area.ASO, CRP and RF higher values of patiens were significantly decreased ($p < 0.05$ and $p < 0.01$). Knee, joint, calf, hip, shoulder, upper back, low back (lumbago), tailbone and fibromyalgia paints of patients were significantly reduced ($p < 0.05$ and $p < 0.01$).Squill bulb constituents can reduce the musculoskeletal pains.

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Keywords: Squill bulb *(Urginea maritima)* (L.) Baker, scilliroside, taxifolin, proscillaridin-A**,** lumbago, fibromyalgia, pain

1. Introductıon

Urginea maritima (Liliaceae) is cultivated in the Mediterranean area. It is used as a cardiotonic diuretic in Europe for the treatment of cardiac marasmus and edema. Squill (white sea onion) is a cardiotonic similar to digitalis. It has been also used in hair tonics to treat seborrhea and dandruff, as a cancer remedy and a rodenticide. Squill has been studied for its cardiovascular effects at an intra venous dose of methylproscillaridin 1 mg (a cardiac glycoside of the herb). Classical use of the dried bulb was at 100 mg doses. Like any cardiac glycoside-containing product, the sufficient caution should be paın in use of squill caution. Adverse reactions, including vomiting and convulsions, are generally observed in overdose situations. Squill extracts cause peripheral vasodilation and bradycardia in anesthetized rabbits. Squill glycosides have cardiotonic properties similar to digitalis. However, squill components are generally poorly absorbed from the gastrointestinal tract and are less potent than digitalis. Preparations for oral administration are enteric-coated to prevent degradation by gastric acid. Meproscillaren, a semisynthetic derivative of proscillaridin, is absorbed orally and may be effective in some patients. The strength of squill preparations and extracts may vary and therefore, these preparations must be used with caution [1-8]. Methanolic extracts of red squill have been used as hair tonics in treating seborrhea and dandruff. In general, red squill is not used medicinally and the powdered dried bulbs of red squill are mainly used as rodenticides, which are in the glycoside family of chemicals. It is a botanical compound extracted from the bulb of the Mediterranean squill plant. As it is used effectively against Norway rats, it was also used to control black rats, house mice, long-tailed field mice, and field voles. Scilliroside is a highly toxic chemical. The dose at which half of the test animals die,

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the oral LD_{50}, is 0.43 mg/kg for female rats, 0.7 mg/kg for male rats, and 0.35 mg/kg for mice. Pigs and cats survived doses of 16 mg/kg. Scilliroside is irritating to the skin. Scilliroside affects heart muscle contractions. Scilliroside is moderately toxic to some birds. Fowl survive doses of 400 mg/kg/day. Certain birds learn to avoid insects contaminated with scilliroside because of its strong emetic characteristic [1-15].

2. Materıals and methods

Squill bulbs *(Urginea maritima) (L.) Baker (*Familia: *Liliaceae*) were collected in Silifke and in Anamur coasts, Turkey during summer and autumn months. This study was mainly conducted in the according to patient's own wishes and their applications living on the Silifke and Anamur coasts in Turkey in summer and autumn months of 2008 and 2009. Most of the information was collected from the people residing in Büyükeceli (Silifke) and Anamur. According to the speech of patients, they have applied voluntarily to the body these applications in previous years. On the other hand, patients were doing more planned this application. Chemicals has been described scilliroside ($C_{32}H_{44}O_{12}$), proscillaridin-A ($C_{30}H_{42}O_8$) and taxifolin ($C_{15}H_{12}O_7$) and other chemicals from squill bulb *(Urginea maritima)* (L.) Baker in patients. These applications were recommended to planned. Study approval was received from University Ethics Committee. Firstly, themselves removed by digging the tubers from soil and squill lumps are divided into two lumps onion. After, they applied the onion slices to their feet especially approximately 10 and 30 minutes and moreover their arms and shoulders, Sometimes patients are applied squill lumbs longer than an hour. Patients are repeated this application in every autumn and especially summer. Rheumatic and paralytic patients are more applicable than patients. According to speech, rheumatic pains of patients have been significantly decreased. In this study, 250 patients were monitored in coats. The average age of these patients were between 40 and 74 years old. Of these 100 were male and 150 female patients.

Data were obtained through field survey conducted from May to October months in 2008 and 2009 years by performing interview through structured questionnaire with selected people (Informants). These informants were local herbalists, healers, farmers, and midwives. The Informants are between 40 – 74 age groups. The selection of Informants was based on their recognition as experts and knowledgeable members concerning folk medicine. We ask the informants whether they use humans in the healing practices. We also ask the modes of preparation of remedies and how the medicines are administered, since this kind of information indicates how a given medicine can be therapeutically efficient in terms of the right ingredients, the proper dose, and the right length of preparation. According to them, their knowledge of folk medicine was acquired mainly through parental heritage. The interviews were recorded and documented. Pain assessment was made according to the speech of patients. Furthermore, 60 of % proscillaridin-A ($C_{30}H_{42}O_{8,}$ molecular weight 530.66 g/mol), taxifolin ($C_{15}H_{12}O_{7,}$ molecular weight 304.25 g/mol) and scilliroside ($C_{32}H_{44}O_{12}$, Molecular mass is 620.685 g/mol) (Merck) solution in pure glycerin was applicate as external on the pain area [1,2,4,7,13,14,15].

Mainly constituents of squill bulb *(Urginea maritima)* (L.) Baker. Squill contains cardiac glycosides (0.15 - 2.4% bufadienolides, including scillaren A), flavonoids, anthocyanidins, and mucilage. The cardiac glycosides are strongly diuretic and relatively quick-acting. They do not have the same cumulative effect as those in foxglove. The following list of constituents have been reported to be found in the bulb of the plant:

Chelidonic-acid, Cyanidin-3-caffeoyl-glucoside, Cyanidin-3-glucoside, Dihydroquercetin Dihydroquercetin-4'-monoglucoside, Gallic-acid, Glucoscillaren-a, Glucoscilliphaeoside, Glucosinistrin, Isorhamnetin, Kaempferol-3-0-glucoside,Kaempferol-3-trıglucoside, Kaempferol-7-glucoside, Kaempferol-7-glucoside-3-diglucoside, Kaempferol-7-glucoside-3-rhamnoglucoside,Kaempferol-7-glucoside-3-trıglucoside,Kaempferol-7-rhamnoside-3-rhamnoglucoside, Leucocyanidin, P-coumaric-acid,Pelargonidin-monoglucoside,Phytosterols Proscillaridin-A Quercetin Quercetin-3-monoglucoside), Quercitrin,Scillaren-A, Scillarenin-A Scillarenin-beta-d-glucoside,Scillaridin-A, Scillazuroside, Scillicoeloside, Scillicyanoside ,Scilliglaucoside, ScillİkryptoSide, Scillin Scilliphaeoside, Scillipicrin Scilliroside, 6ß-Acetoxy-3ß-

(ß-D-glukopyranosyloxy)-8,14-dihydroxy-5ß-bufa-4,20,22- trienolid, Scillirosidine, Scillirubroside, Scillirubrosidine, Scillitoxin, Sinistrin, Taxifolin [2,3,4,5,12,13,14,15].

3. Results

Pain biographies of patiens were initially checked (Table 1). Other tests were performed after. Anti-Streptolysin O (ASO), Rheumatoid Factor (RF) and C-Reactive Protein (CRP) normal and range values were given Table 2.

Table 1. Generally check of pain problems of patients.

	Better	Worse	No Change		Better	Worse	No Change
Coughing / Sneezing	[x]	[ ]	[ ]	Bending Forward	[ ]	[x]	[ ]
Straining	[ ]	[ ]	[x]	Bending Backward	[x]	[ ]	[ ]
Standing	[ ]	[x]	[ ]	Lying on Back	[x]	[ ]	[ ]
Walking	[ ]	[ ]	[ ]	Lying on Stomach	[ ]	[ ]	[x]
Sitting	[x]	[ ]	[ ]	Overhead Reaching	[ ]	[x]	[ ]
Lifting	[ ]	[x]	[ ]	Squatting	[ ]	[x]	[ ]
Pushing/ Pulling	[ ]	[x]	[ ]	Kneeling	[ ]	[x]	[ ]
Driving	[x]	[ ]	[ ]	Typing / Writing	[ ]	[ ]	[x]
During Activity	[x]	[ ]	[ ]	After Activity	[ ]	[x]	[ ]

Table 2. Mean and range values of ASO, RF and CRP.

	Mean	Range
ASO	154 U/ml	108-200 U/ml
RF	36 U/ml	25-47 U/ml
CRP	1.0 mg/dl	0.7-1.3 mg/dl

Table 3. Effects of scilliroside ($C_{32}H_{44}O_{12}$) from squill bulb on some painful areas and biochemical parameters.

Age	Improvement status in the painful area and biochemical data							
	Knee	Joint	Shank	Hip	Shoulder	AS0 U/ml B/A	CRP mg/dl B/A	RF U/ml B/A
40 (n=5)	PCD	PCD	RPH	PCD	RPH	287/164**	12/17*	87-47**
45 (n=17)	PCD	PCD	RPH	PCD	RPH	295/172**	8/1**	76-29**
54 (n=45)	PCD	RPH	RPTT	PCD	PRTT	277/148**	7/1**	87-54**
65 (n=60)	RPH	PRTT	RPTT	PCD	PRTT	297/178**	9/2**	75-37**
70 (n=10)	RPH	PRTT	PC	RPTT	RPH	300/189**	13/2**	69-48**
74 (n=13)	PRTT	PC	NC	PC	PRTT	324/201**	11/3**	65-48**
Control (n=10)	No pain	No pain	No pain	No pain	No pain	120	1	30

Significantly degrees are *P < 0.05 and **P < 0.01, PCD : Pain completely disappeared. This was accepted by one hundred percent(100%). RPH: Reduction in the amount of pain of by half (50 %), PRTT: Pain was reduced from time to time, PC: Pain continues, NC : Not curable , ASO : Anti-Streptolysin O, RF: Rheumatoid Factor and CRP : C-Reactive Protein , B/A : B is squill bulb before application, A is after application squill bulb

Table 4. Effects of scilliroside ($C_{32}H_{44}O_{12}$) from squill bulb on some painful areas and biochemical parameters.

Age	Improvement status in the painful area and biochemical data							
	Arm and hand	Upper back	Low back (lumbago)	Tailbone	Fibromyalgia	AS0 U/ml B/A	CRP mg/dl B/A	RF U/ml B/A
40 (n=5)	PCD	PCD	RPH	PCD	PCD	137/84**	5/1**	65/27**
45 (n=17)	PCD	PCD	PCD	RPH	RPH	164/98**	7/2**	74/45**
54 (n=26)	RPH	RPH	PCD	PCD	PRTT	175/96**	9/3**	86/38**
65 (n=35)	RPH	RPH	PCD	PRTT	PRTT	156/80**	8/1**	77/48**
70 (n= 8)	RPH	PRTT	PRTT	PC	PC	190/73**	5/2**	96/52**
74 (n= 9)	PRTT	PRTT	PRTT	PRTT	NC	195/94**	7/1**	74/58**
Control (n=10)	No pain	No pain	No pain	No pain	No pain	120	1	30

Significantly degree is **P < 0.01, PCD : Pain completely disappeared. This was accepted by one hundred percent(100%), RPH: Reduction in the amount of pain of by half (50 %), PRTT: Pain was reduced from time to time, PC: Pain continues, NC : Not curable , ASO : Anti-Streptolysin O, RF: Rheumatoid Factor and CRP : C-Reactive Protein , B/A : B is squill bulb before application, A is after application squill bulb

Table 5. Effects of 60 of % proscillaridin-A ($C_{30}H_{42}O_8$) from squill bulb on some painful areas and biochemical parameters.

Age	Improvement status in the painful area and biochemical data							
	Knee	Joint	Shank	Hip	Shoulder	AS0 U/ml B/A	CRP mg/dl B/A	RF U/ml B/A
40 (n=5)	PCD	PCD	RPH	PCD	RPH	287/154**	12/18*	87-45**
45 (n=17)	PCD	PCD	RPH	PCD	RPH	295/175**	8/3**	76-30**
54 (n=45)	PCD	RPH	RPTT	PCD	PRTT	277/142**	7/2**	87-53**
65 (n=60)	RPH	PRTT	RPTT	PCD	PRTT	297/180**	9/1**	75-31**
70 (n=10)	RPH	PRTT	PC	RPTT	RPH	300/190**	13/3**	69-45**
74 (n=13)	PRTT	PC	NC	PC	PRTT	324/201**	11/2**	65-44**
Control (n=10)	No pain	No pain	No pain	No pain	No pain	120	1	30

Significantly degrees are *P < 0.05 and **P < 0.01, PCD : Pain completely disappeared. This was accepted by one hundred percent(100%), RPH: Reduction in the amount of pain of by half (50 %), PRTT: Pain was reduced from time to time, PC: Pain continues, NC : Not curable , ASO : Anti-Streptolysin O, RF: Rheumatoid Factor and CRP : C-Reactive Protein , B/A : B is squill bulb before application, A is after application squill bulb

Table 6. Effects of 60 of % taxifolin ($C_{15}H_{12}O_7$) from squill bulb on some painful areas and biochemical parameters.

Age	Improvement status in the painful area and biochemical data							
	Arm and hand	Upper back	Low back (lumbago)	Tailbone	Fibromyalgia	AS0 U/ml B/A	CRP mg/dl B/A	RF U/ml B/A
40 (n=5)	PCD	PCD	RPH	PCD	PCD	137/82**	5/2**	65/23**
45 (n=17)	PCD	PCD	PCD	RPH	RPH	164/88**	7/1**	74/44**
54 (n=26)	RPH	RPH	PCD	PCD	PRTT	175/90**	9/2**	86/35**
65 (n=35)	RPH	RPH	PCD	PRTT	PRTT	156/76**	8/2**	77/45**
70 (n= 8)	RPH	PRTT	PRTT	PC	PC	190/72**	5/1**	96/57**
74 (n= 9)	PRTT	PRTT	PRTT	PRTT	NC	195/89**	7/1**	74/56**
Control (n=10)	No pain	No pain	No pain	No pain	No pain	120	1	30

Significantly degree is **P < 0.01, PCD : Pain completely disappeared. This was accepted by one hundred percent(100%), RPH: Reduction in the amount of pain of by half (50 %), PRTT: Pain was reduced from time to time, PC: Pain continues, NC : Not curable , ASO : Anti-Streptolysin O, RF: Rheumatoid Factor and CRP : C-Reactive Protein , B/A : B is squill bulb before application, A is after application squill bulb

Table 7. Effects of 60 of % taxifolin ($C_{15}H_{12}O_7$) from squill on some painful areas and biochemical parameters.

Age	Improvement status in the painful area and biochemical data							
	Knee	Joint	Shank	Hip	Shoulder	AS0 U/ml B/A	CRP mg/dl B/A	RF U/ml B/A
40 (n=5)	PCD	PCD	RPH	PCD	RPH	287/162**	12/9*	87-44**
45 (n=17)	PCD	PCD	RPH	PCD	RPH	295/176**	8/2**	76-27**
54 (n=45)	PCD	RPH	RPTT	PCD	PRTT	277/139**	7/2**	87-48**
65 (n=60)	RPH	PRTT	RPTT	PCD	PRTT	297/174**	9/2**	75-35**
70 (n=10)	RPH	PRTT	PC	RPTT	RPH	300/175**	13/3**	69-42**
74 (n=13)	PRTT	PC	NC	PC	PRTT	324/176**	11/2**	65-43**
Control (n=10)	No pain	No pain	No pain	No pain	No pain	120	1	30

Significantly degrees are *P < 0.05 and **P < 0.01, PCD : Pain completely disappeared. This was accepted by one hundred percent(100%), RPH: Reduction in the amount of pain of by half (50 %), PRTT: Pain was reduced from time to time,PC: Pain continues, NC : Not curable , ASO : Anti-Streptolysin O, RF: Rheumatoid Factor and CRP : C-Reactive Protein , B/A : B is squill bulb before application, A is after application squill bulb

Table 8. Effects of 60 of % proscillaridin-A ($C_{30}H_{42}O_8$) from squill bulb on some painful areas and biochemical parameters.

Age	Improvement status in the painful area and biochemical data							
	Arm and hand	Upper back	Low back (lumbago)	Tailbone	Fibromyalgia	AS0 U/ml B/A	CRP mg/dl B/A	RF U/ml B/A
40 (n=5)	PCD	PCD	RPH	PCD	PCD	137/77**	5/1**	65/23**
45 (n=17)	PCD	PCD	PCD	RPH	RPH	164/88**	7/2**	74/39**
54 (n=26)	RPH	RPH	PCD	PCD	PRTT	175/87**	9/1**	86/32**
65 (n=35)	RPH	RPH	PCD	PRTT	PRTT	156/76**	8/2**	77/38**
70 (n= 8)	RPH	PRTT	PRTT	PC	PC	190/75**	5/1**	96/48**
74 (n= 9)	PRTT	PRTT	PRTT	PRTT	NC	195/89**	7/1**	74/47**
Control (n=10)	No pain	No pain	No pain	No pain	No pain	120	1	30

Significantly degree is **P < 0.01, PCD : Pain completely disappeared. This was accepted by one hundred percent(100%), RPH: Reduction in the amount of pain of by half (50 %), PRTT: Pain was reduced from time to time, PC: Pain continues, NC : Not curable , ASO : Anti-Streptolysin O, RF: Rheumatoid Factor and CRP : C-Reactive Protein , B/A : B is squill bulb before application, A is after application squill bulb

4. Discussion

Major urginea constituents of concern are the glycosides of the bufadienolide type. From bulbs of *Urginea maritima* aggregate a large number of bufadienolides have been isolated. Constituents were scilliroside, the predominant active glycoside scillarenin, 3-O-beta- D-glycoside, proscillaridin A, scilliphaeosidin- 3-O-beta-D-glycoside, scilliglaucoside, scilliphaeoside,12-epi- scilliphaeoside, glucoscilliphaeoside, 12-epigluco scilliglaucoside,12-beta-hydroxyscilliglaucosidin-3-O-beta-D-glycoside, 12-epi-scilliphaeosidin-3-O-beta-D-glycoside,12-episcillinphaeosidin-3-O-alpha-L-rhamnosido-alpha-L-rhamnoside, scillaren A, gamabufotalin-3-O- alpha-L- rhamnoside, scilliglaucoside, scillirubrosidin-3-O- alpha-L- rhamnoside, scillirubroside-3-O-alpha-L-rhamnoside, scillirubroside, 12-beta-hydroxyscilliroside, 5-alpha-4,5-alpha-dihydroscillirosidin 3-O-alpha-L-thevetosido-beta-D-glucoside, deacetylscilliroside, 10-carboxy-5-beta-14-beta-dihydroxybufa-3,20,22-trienolide-5-O-beta-D-glucoside, scilliglaucogenin. Further constituents of *Urginea maritima* and *Urginea numudica* are anthocyanes, flavonoids, fatty acids and polysaccharides.The bufadienolide glycoside content in the mother tincture is in the range of 0.04 to 0.07 %. This corresponds to a maximum content of 0.0021% (21 µg/ml) in the 1:100 dilution [1,2,3,7,9,10,11].

The pharmacologically active principles of *Urginea maritima* are the cardiotrophic steroidal bufadienolide glycosides. Number and species on the bound sugar moieties and the number of oxygen atoms in the aglycone determine the pharmacological activity of bufadienolide glycosides, which exert their action mainly by inhibition of membranous adenosine triphosphatase of cardiomuscular tissue. Cardiac glycosides act positive inotropic and negative chronotrophic. Cardiac glycosides and aglyconesand together, cardiac glycosides and aglycone derivatives are classified as cardenolides. Cerberoside is a cardiotonic compound found in thevetia. Chemicals with digitalic activity include: Cactine Cassaidine Cerberin Cheirotoxin Erythrophleguine Hellebrin K-Strophanthoside Lanatoside-C Peruvoside Thevetin Cardiac glycosides useful in the present invention include, but are not limited to, lanatoside A, desacretyllanatoside A, actyl digitoxin, digitoxin, lanatoside C, desacetyllanatoside C, digoxin, strophanthoside K-strophanthin, ouabain, scillaren A, proscillaridin A, uzarin, digitoxose, gitoxin, strophanthidine-3. beta.-digitoxoside, strophanthidin. alpha.-L-rhamnopyranoside, strophanthidol, oleandrin, acovenoside

A, strophanthidine digilanobioside, strophanthidin-D-cymaroside, digitoxigenin-L- rhamnoside digitoxigenin theretoside, and the like. Aglycones include, but are not limited to, strophanthidin, digitoxigenin, uzarigenin, digoxigenin, digoxigenin 3,12- diacetate, gitoxigenin, gitoxigenin 3-acetate, gitoxigenin 3,16-diacetate, 16-acetyl gitoxigenin, acetyl strophanthidin, ouabagenin. 3-epidigoxigenin, and the like. Preferably the cardiac glycoside is ouabain, digoxin, or digitoxin. In a preferred practice, the cardiac glycoside is ouabain, and the aglycone derivative is strophanthidin. In a more preferred practice the cardiac glycoside is liquid digoxin [4,-15].

Furthermore, a dose dependent constrictor effect on veins has been reported for cats, when treated with an extract (20 % ethanol) obtained from *Urginea maritima.* A diuretic action of the ethanolic extract has been reported for rats and humans.The pharmacokinetic information of *Urginea maritima* relates mainly to the more hydrophobic constituent proscillaridin A. After oral administration of 0.5 mg proscillaridin A, 3 times per day over a period of 14 days, a constant plasma concentration of approximately 0.6 µg/l was observed with a maximum concentration of 0.74 µg/l reached 90 minutes after dosing.For proscillaridin A the main route metabolism has been reported to be conjugation to glucoronic acid and sulphuric acid ana subsequent biliary excretion. Only 4 µg/l of proscillaridin A per day were excreted with the urine. The termal elimination half-life was about 23 hours.In general overall oral absorption rate of 25 to 50 % has been reported for glycosides from *Urginea maritima*. Data on acute toxicity is available fort he dried drug powder (standardised squil powder) and some constituents of *Urginea maritima*. Intravenous LD values were reported as 0.55 mg/kg in guinea pigs and 28 mg/kg bw (body weight) in cats for proscillaridin A, 0.41 mg/kg bw in guinea pigs and 0.20 mg/kg bw in cats for scillaren A, while for scilliroside 0.15 mg/kg bw were observed in rats and 0.12 mg/kg bw in cats. Oral LD_{50} values for scilliroside were 0.5 and 0.7 mg/kg bw in rats and less than 20 mg/kg bw in dogs and pigs, and oral LD value in rats was 2 to 4 mg/kg bw. Higher lethality to female rats compared to male rats was reported by several authors with a toxicity ratio 1:3. Large differences in toxicity of red squill powder have been noted for chickens, rabbit and guinea pigs with rabbits being most susceptible to lethal effects. These differences can be partly explained by species differences in the pattern of micro-organisms in the gastrointestinal tract. This can produce hydrolysing enzymes that split the sugar moieties from the aglycones, which then are more readily absorbed. For standardised squill powder, which has a glycoside content equivalent to an activity of 0.2 % proscillaridin A, the oral LD_{50} values were given as 320 mg/kg bw for guinea pigs, 490 mg/kg bw for rats, 100 to 500 mg/kg bw for cattle and horses, 145 mg/kg bw for dogs and cats and 250 to 500 mg/kg bw for sheep. The human pytotherapy the dried bulb of the white variety *Urginea maritima* (squill) is used orally as diuretic, emetic, expectorant and cardiotonic. Daily oral doses for adults range from 30 to 500 mg/kg (the standardised drug is adjusted to an activity equivalent approximately 0.2 % of proscillaridin A). The main symptoms of oral doses are disorders of gastrointestinal tract like nausea,vomiting, diarrhoea, as well as irregular pulse.Intoxication with fatal outcame has been described when two children (3 and 5 yeras old) ingested inadvertenly a syrup with a content of 0.1 g of the drug. About 1.5 g of the drug is reported to be lethal for adults [3-15].

Taxifolin or dihydroquercetin is a bioflavonoid with a similar structure to that of quercetin. It is extracted from Siberian larch. Over the last 50 years, almost 600 studies (most of them Russian) have investigated its efficacy and safety. In particular, they have highlighted its antioxidant potency and vascular-protective action. Taxifolin has also been shown to benefit cardiovascular health, the skin, cognitive function, inflammation, allergies and immunodeficiency, as well as the health of diabetics. The main mode of administration is topical but cardiac glycosides for the treatment of muscle spasm and pain may also be formulated into pharmaceutical compositions suitable for local, intravenous and systemic application. Time release and topical patch formulations are also possible. Effective concentrations of one or more of the conjugates are mixed with a suitable pharmaceutical carrier or vehicle. The concentrations or amounts of the conjugates that are effective requires delivery of an amount, upon administration, that ameliorates the symptoms or treats the disease. Typically, the compositions are formulated for single dosage administration. Therapeutically effective concentrations and amounts may be determined empirically by testing the conjugates in known in vitro and in vivo systems, such as those described herein; dosages for humans or other animals may then be extrapolated therefrom Other

diseases associated with muscle spasm and pain that may be treated with cardiac glycosides include but are not limited to: Complex Regional Pain Syndromes, Fibromyalgia, Spastic Torticollis, Low Back Pain, General Myofascial Pain, Neuropathic Pain, Muscle Spasm and Pain secondary to pregnancy, Amyotrophic lateral sclerosis, Cerebral palsy, Cramps, stroke, multiple sclerosis, cerebral palsy, neurodegenerative diseases, trauma, spinal cord injury, and nervous system poisons such as strychnine, tetanus, and certain insecticides. Nerve damage may lead to a prolonged or permanent muscle shortening called contracture. However, most muscle spasms are not caused by disease, but more commonly by physical activity or stress. Relaxation of a muscle actually requires energy to be expended. The energy is used to recapture calcium and to unlink the actin and myosin. This causes the muscles fibers to lengthen because the unlinked chains slide back to their resting positions. Normally, sensations of pain and fatigue signal that it is time to slow down or stop. Resting allows the muscles to restore their supplies of energy. Ignoring or overriding those warning signals can lead to such severe energy depletion that the muscle cannot be relaxed, causing a cramp. The lack of blood flow deprives the muscles of their source of energizing oxygen and nutrients and removal of fatigue causing waste. The pain of a muscle cramp is intense, localized, and often debilitating. Coming on quickly, it may last for minutes and fade gradually. Contractures develop more slowly, over days or weeks, and may be permanent if untreated. Fasciculations may occur at rest or after muscle contraction, and may last several minutes. Chronic pain is devastating and demoralizing and causes numerous adverse effects, including insomnia, anxiety, impaired concentration and depression. [2-14].

5. Conclusıons

Constituents of *(Urginea maritima)* (L.) Baker can develop as biodrug or pharmacological. Analgesic endication of squill bulb can be useful in decreasing of various pains. But, squill bulbs have very toxic constituents.Contrendication and adverse effects of this plant are very important in clinical evaluations.Analgesic ef fects of constituents of squill bulb *(Urginea maritima)* (L.) Baker on various pain must investigate both pharmacological and physiological.

References

[1] M. Fernandez, F.A. Vega, T. Arrupe, J. Renedo. Phytochemistry, **11**, 1534 (1972).
[2] M. Iizuka, T. Warashina, T. Noro. Chem Pharm Bull.,**49**, 282 (2001).
[3] B. Kopp, L. Krenn, M. Draxler, A. Hoyer, R. Terkola, P. Val- laster, W. Robien. Phytochemistry **42**, 513 (1996).
[4] L. Krenn, B.Kopp, A.Deim, W.Robien and W.Kubelka. Planta Medica, **60,** 63 (1994).
[5] L.Krenn and B. Kopp. J Nat Prod. **59**, 612 (1996).
[6] L. Krenn, M. Jelovin, B. Kopp. Fitoterapia, **71**, 126 (2000).
[7] A. Margaret, M.D.Caudill. Managing Pain Before It Manages You. Comprehensive program for living with chronic pain. Practical exercises focus on setting goals and solving problems. New York: Guilford Press (2001).
[8] M. Iizuka, T. Warashina and T. Noro. Chem. Pharm. Bull. **49**(3), 282 (2001).
[9] VMJ Pascual and M. Fernández. Ind. Crops Products, **10**, 115(1999).
[10] W. Praznik, T.Spies. Carbohydr Res. **243**, 91 (1993).
[11] R.S. Rapaka, R.L. Hawks. Opioid Peptides:Molecular Pharmacology, Biosynthesis, and Analysis. NIDA Research Monograph 70. National Institute on Drug Abuse 5600 Fishers Lane Rockville, Maryland 20857,pp.1-424 (1986).
[12] T. Spies, W. Praznik, A. Hofinger, F. Altmann, E. Nitsch, R. Wutka. Carbohydr Res.,**235**, 221 (1992).
[13] http://www.emea.europa.eu/pdfs/vet/mrls/060399en.pdf , EMEA(The European Medicines Agency).The European Agency for the Evaluation of Medicinal Products.Veterinary Medicines Evaluation Unit.(EMEA)/ MRL/ 603/99 FINAL, p.1-4, (2000).
[14] A. J. Verbiscar, T.F.Banigan and H.S.Gentry. Recent research on red squill as a rodenticide.

p. 51–56. In: T.P. Salmon (ed.), Proceedings twelfth vertebrate pest conference. Univ. California, Davis, USA, (1986a).
[15] A. J. Verbiscar, J. Patel, T.F.Banigan and R.A. Schatz. J. Agr. Food Chem., **34**, 973 (1986b).