IJPSR (2016), Vol. 7, Issue 3 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 September, 2015; received in revised form, 12 November, 2015; accepted, 23 January, 2016; published 01 March, 2016

A PILOT STUDY TO ASSESS THE EFFICACY AND SIDE EFFECTS OF SILYMARIN ALONE AND IN COMBINATION WITH ALENDRONATE IN TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

M. H El-Hamamsy [1], H. G. Eltoukhy [*2] and M. M. Hasanein [3]

Professor of Clinical Pharmacy [1], Faculty of Pharmacy, Ain-Shams University, Cairo, Egypt.
Department of Pharmacy Practice and Clinical Pharmacy [2], Faculty of Pharmaceutical Sciences & Pharmaceutical Industries, Future University in Egypt, Cairo, Egypt.
Associate Professor of Orthopedics [3], Faculty of Medicine, Cairo University, Egypt.

Keywords:

Postmenopausal osteoporosis, Silymarin, Alendronate. Clinical pharmacy

Correspondence to Author:
H. G. Eltoukhy

The Future University in Egypt, End of 90th street, fifth settlement, New Cairo, Egypt.

Email: heltoukhy@ymail.com

ABSTRACT: Background: Currently oral bisphosphonates such as alendronate are the preferred therapeutic option for the treatment of postmenopausal osteoporosis by increasing bone mineral density and decreasing both vertebral and non-vertebral fracture risk. Silymarin is mainly used as hepato-protectant but in recent studies on ovariectomized rats, it was found that silymarin can be a promising antiosteoporotic pharmacological agent and selective estrogen receptor modulator. **Objective:** To evaluate the clinical outcome of combination therapy of alendronate and silymarin on postmenopausal osteoporotic women compared to the monotherapy of each. **Methods:** This was prospective, interventional, randomized study. A total of 69 patients were classified into 3 groups: Group1 (n=22) received 70 mg alendronate tablet once weekly for two years, Group 2 (n=23) received 140 mg silymarin capsule three times daily for two years, Group 3 (n=24) received 35 mg alendronate once weekly and 140 mg silymarin three times daily for two years. The bone mineral density of the patients was monitored using DXA scan at 0,1 and 2 years. **Results:** Silymarin showed improvement in the mean T-scores of spine, femur and wrist after two years of treatment, this improvement was significantly less than in patients treated with alendronate or combined therapy($p_{spine}=0.000$ $p_{femur}=0.000$ $p_{wrist}=0.003$) where the p value represents the significance difference between the three groups after two years of treatment. **Conclusion:** To consider Silymarin alone as an efficient medication for postmenopausal osteoporosis, it requires further studies for longer time frames, dose assessment and larger patient groups

INTRODUCTION: Osteoporosis describes a state in which bone is fully mineralized but its structure is abnormally porous and its strength is less than normal for a person of that age and sex, also there is a significant decrease in bone mass per unit volume of bone tissue and this is accompanied by increased fragility of the bone [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.7(3).1012-20

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.7 (3).1012-20

Postmenopausal osteoporosis: women at the age of menopause and for the next 10 years lose bone at an accelerated rate (about 3% per year) compared with 0.3% during the preceding decade, this is mainly due to increased bone resorption, the withdrawal of estrogen have removed one of the normal restraints of osteoclastic activity.

In some cases this process is exaggerated and results in osteoporosis and skeletal failure [2]. There are two types of osteoporosis primary and secondary. Primary osteoporosis is caused by reduction in estrogen in a woman's body after menopause (type 1), while secondary osteoporosis

is caused by age related changes in the rate of bone building that occurs in both men and women as they grow older (type 2). Secondary osteoporosis is also caused by certain medical conditions and treatments as well as by unhealthy behaviors [1].

Alendronate is one of the most widely used drugs today. Millions of people have used it and doctors continue to prescribe it even though there are many other osteoporosis drugs on the market. Alendronate can increase bone mineral density and counteract the disease osteoporosis. Alendronate is classified as a bisphosphonate drug, like other medications in this class alendronate inhibits bone resorption via action on osteoclasts or on osteoclast precursors. There are other antiresorptive agent used in treatment of osteoporosis like selective estrogen receptor modulators (SERMS) and calcitonin [3].

Silymarin is an ancient medicinal plant which has been used for centuries for treatment of different diseases such as liver and gallbladder disorders, protecting liver against snake bite and insect stings, mushroom poisoning and alcohol abuse [4]**.** Recently it has been used in prevention and treatment of cancers [5]**,** renal protection [6], in treatment of Alzheimer disease [7]**.** It also has protective effect on pancreas and immunomodulation effects [8]**,** preventing effect against hemolysis [9] and protective effect against environmental toxins [10] in addition to that silymarin is considered as a promising pharmacological agent as antiosteoporotic and selective estrogen receptor modulator [7]. This study is aimed to evaluate the clinical outcome of combination therapy of silymarin and alendronate on postmenopausal osteoporotic patients compared to monotherapy of each.

Patients and Methods:

Study design and setting:

This is a prospective, interventional, randomized pilot study that was conducted on 69 postmenopausal females whom were selected from the orthopaedic outpatient department at Qasr Al-Ainy hospital Cairo University, Cairo, Egypt in the period from May 2011 till September 2013

Inclusion criteria: We included in the study postmenopausal females within 10 years of starting menopause, females who suffered from previous low energy fractures at the menopause, patients with no known associated medical conditions according to history and general examination (renal, hepatic, thyroid disorders etc.).

Baseline DXA scan was done for patients who fitted these criteria and only patients who displayed T-scores indicating osteoporosis were randomized into their respective groups and treatment started

Exclusion criteria:

We excluded from the study cases with known secondary osteoporosis (eg. Steroid related), Patients who have started menopause more than 10 years ago, Patients with pre-existing medical conditions (renal, hepatic), Patients with chronic drug intake, Patients with kyphotic deformity of the vertebrae, Premature menopausal patients (menopausal patients before the age of forty).

Patients:

Patients were randomly categorized into 3 groups: Group 1 (n=22) included patients who received 70 mg weekly dose of alendronate (osteonate) for two years, Group 2 (n=23) included patients who received silymarin 140 mg (legalon) 3 times daily for two years, Group 3 (n=24) included patients who received 35 mg weekly dose of alendronate (osteonate) and 140 mg 3 times daily of silymarin (legalon) for two years. Baseline DXA scans was done for all the patients and follow up was done at 6 months post treatment, one year post treatment and at the end of the treatment cycle.

Approval for the study protocol for both the scientific and the ethical aspects was obtained from the committee of Ethics of Faculty of Pharmacy, Ain Shams University and the Scientific Committee for Clinical Research of Al Qasr Al-Aini hospital. An informed consent was obtained directly from each participant.

Clinical follow up of patients and data collected:

The clinical pharmacists in the study were responsible for all steps of clinical assessment and patient follow up. In the initial phase of the study candidates were interviewed and counseled about the idea of the study. Candidates who agreed to participate signed consent and were given a

questionnaire to fill out. The first part of the questionnaire included baseline demographics, menstrual history, history of previous fractures and bone pains, medication history, disease history and social history [11]. After establishing a diagnosis of osteoporosis the patients were randomized into their respective groups.

All patients were then provided with information about osteoporosis such as: what is osteoporosis, what are risk factors of osteoporosis what is bone mineral density testing and what are the medications used to treat osteoporosis which are mainly bisphosphonates, patients of alendronate group were educated about the precautions of intake of bisphosphonates. Compliance to treatment and dosing regimen was checked by using the pill count method where the patients were asked to bring the empty strips with them and number of missed doses was calculated.

During the every month visit it was also important to review the history of osteoporotic fractures and bone pains and to check if any side effects appeared. A checklist was used to record side effects occurance (**Table 1**).

After one year and two years of treatment DXA scans were done to evaluate the improvement of T-scores values in spine, femur, and wrist of all patients in different groups then the results of DXA scans from the beginning of treatment till the end of treatment were compiled to display the results of the study.

TABLE 1: CHECKLIST FOR THE MOST COMMON TREATMENT RELATED ADVERSE DRUG REACTIONS OF ALENDRONATE AND SILYMARIN [12, 13].

Adverse drug reaction of Alendronate	Yes	No	Adverse drug reaction of Silymarin	Yes	No
Abdominal pain			Gentle gastrointestinal disturbance		
Dyspepsia			Laxative symptoms		
Constipation			Nausea		
Diarrhea			Urticaria		
Flatulance			Itching		
Oesophageal ulcer			Headache		
Acid regurgitation			Joint pain		
Nausea					
Headache					
Dizziness					
Muscloskeletal pain					

Statistical Analysis:

Data was coded and entered using statistical package SPSS version 15. Data was summarized using mean and standard deviation. Comparison between the groups were done using non parametrical Kruskal Wallis test for quantitative variables which are not normally distributed. P-values less than or equal 0.05 were considered as statistically significant.

RESULTS: In total, 75 patients with postmenopausal osteoporosis were included only 69 of them completed the study. All patients were recruited from outpatient orthopeadics clinic at Qasr Alainy Cairo University. The population of the study was categorized into three groups: group 1 (n=22) where patients received 70 mg Alendronate once weekly for two years, group 2 (n=23) where patients received 140 mg Silymarin three times daily for two years and group 3 (n=24) where patients received 35 mg Alendronate once weekly and 140 mg Silymarin three times daily for two years. Then DXA scans were done after one year of treatment and after two years of treatment.

TABLE 2: DEMOGRAPHIC CHARACTERISTICS OF POSTMENOPAUSAL OSTEOPOROTIC PATIENTS (N=69

	Alendronate Group (Group1) n=22	Silymarin Group (Group 2) n=23	Alendronate and Silymarin Group (Group 3) n=24	Significance
Age in years (mean ± SD)	57.22±3.96*	56.47±4.19*	58.83±2.66*	P=0.085 nonsignificant
Weight in kg (mean ± SD)	75.73±8.06*	77.78±8.86*	77.29±8.56*	P=0.701 nonsignificant

Demographic comparison between the three groups as represented in Table 1 showed no statistically significant difference in age and weight ($p>0.05$)

*Data are expressed as mean and standard deviation *n; number of patients*

There is a significantly larger increase in the % change of T-scores of Alendronate and Combined therapy groups than in the Silymarin group as shown in **Table 3.**

TABLE 3: THE CHANGES IN THE MEAN VALUES OF T-SCORES OF SPINE IN THE STUDIED GROUPS BEFORE TREATMENT AND AFTER 1 AND 2 YEARS OF TREATMENT USING KRUSKAL WALLIS TEST.

	Group 1 n=22		Group 2 n=23		Group 3 n=24		P value	significance
	Mean	±SD	Mean	±SD	Mean	±SD		
Before treatment	-3.26	±0.89	-3.48	±1.02	-3.25	±0.99	P_0 0.55	NS
After 1 year treatment	-2.80	±0.86	-3.37	±1.09	-2.92	±1.13	P_1 0.089	NS
After 2 years treatment	-2.43	±0.87	-3.29	±1.13	-2.70	±1.16	P_2 0.021	S
% Change from baseline to year 1	14.47	±7.96	3.88	±9.61	11.82	±13.11	P_3 0.001	S
% Change from baseline to year 2	26.14	±10.20	6.86	±10.30	18.7 5	±17.05	P_4 0.000	S

Group 1; Alendronate Group 2; Silymarin Group 3; Combined therapy

n= number of patients S=significant NS=nonsignificant

P0: p-value when comparing the three groups before treatment
P1: p-value when comparing the three groups after one year of treatment
P2: p-value when comparing the three groups after two years of treatment
P3: p-value when comparing the percentage change between the three groups after 1 year treatment
P4: p-value when comparing the percentage change between the three groups after 2 years treatment
P $\leq$ 0.05 is significant
SD: standard deviation

There is a significantly larger increase in the % change of T-scores of Alendronate and Combined therapy groups than in the Silymarin group as shown in **Table 4.**

TABLE 4: THE CHANGES IN THE MEAN VALUES OF T-SCORES OF FEMUR IN THE STUDIED GROUPS BEFORE TREATMENT AND AFTER 1 AND 2 YEARS OF TREATMENT USING KRUSKAL WALLIS TEST

	Group 1 n=22		Group 2 =23		Group 3 n=24		P value	significance
	Mean	±SD	Mean	±SD	Mean	±SD		
Before treatment	-2.92	±0.79	-3.01	±0.98	-3.21	±1.32	P_0 0.835	NS
After 1 year treatment	-2.50	±0.76	-2.92	±0.97	-2.94	±1.47	P_1 0.348	NS
After 2 years treatment	-2.22	±0.74	-2.48	±1.77	-2.82	±1.50	$P_2$0.190	NS
% Change from baseline to year 1	15.06	±14.05	2.81	±7.96	12.05	±15.89	P_3 0.000	S
% Change from baseline to year 2	24.58	±16.26	12.30	±39.43	16.50	±19.12	P_4 0.000	S

Group 1; Alendronate Group 2; Silymarin Group 3; Combined therapy

n= number of patients S=significant NS=nonsignificant

P0: p-value when comparing the three groups before treatment
P1: p-value when comparing the three groups after one year of treatment
P2: p-value when comparing the three groups after two years of treatment
P3: p-value when comparing the percentage change between the three groups after 1 year treatment
P4: p-value when comparing the percentage change between the three groups after 2 years treatment
P $\leq$ 0.05 is significant
SD: standard deviation

There is a significantly larger increase in the % change of T-scores of Alendronate and Combined therapy groups than in the Silymarin group as shown in **Table 5**,

TABLE 5: THE CHANGES IN THE MEAN VALUES OF T-SCORES OF WRIST IN THE STUDIED GROUPS BEFORE TREATMENT AND AFTER 1 AND 2 YEARS OF TREATMENT USING KRUSKAL WALLIS TEST.

	Group 1 n=22		Group 2 n=23		Group 3 n=24		P value	significance
	Mean	±SD	Mean	±SD	Mean	±SD		
Before treatment	-2.78	±1.04	-3.41	±1.16	-3.16	±1.42	P_0 0.237	NS
After 1 year treatment	-2.40	±1.07	-3.10	±1.19	-2.81	±1.62	P_1 0.233	NS
After 2 years treatment	-2.05	±0.98	-2.90	±1.15	-2.64	±1.66	P_2 0.083	NS
% Change from baseline to year 1	14.84	±14.04	8.97	±13.18	12.10	±12.93	P_3 0.006	S
% Change from baseline to year 2	26.44	±20.03	14.61	±17.29	22.35	±18.15	P_4 0.033	S

Group 1; Alendronate Group 2; Silymarin Group 3; Combined therapy

n= number of patients **S=significant** **NS=nonsignificant**

P0: p-value when comparing the three groups before treatment
P1: p-value when comparing the three groups after one year of treatment
P2: p-value when comparing the three groups after two years of treatment
P3: p-value when comparing the percentage change between the three groups after 1 year treatment
P4: p-value when comparing the percentage change between the three groups after 2 years treatment

P ≤ 0.05 is significant **SD:** standard deviation

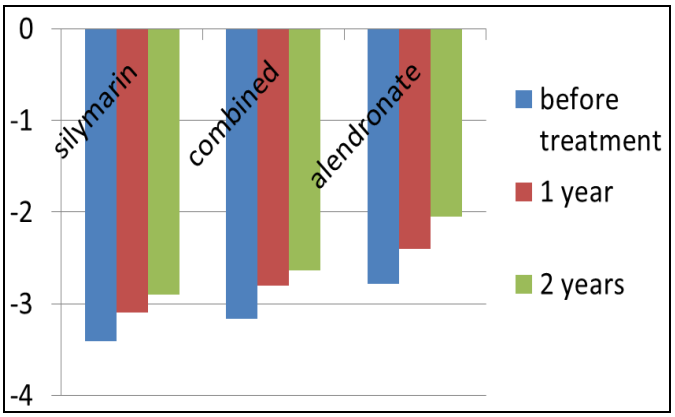

FIG. 1: CHANGES IN T-SCORES DURING THE COURSE OF TREATMENT IN DIFFERENT PATIENT GROUPS AS REGARDS SPINE BMD.

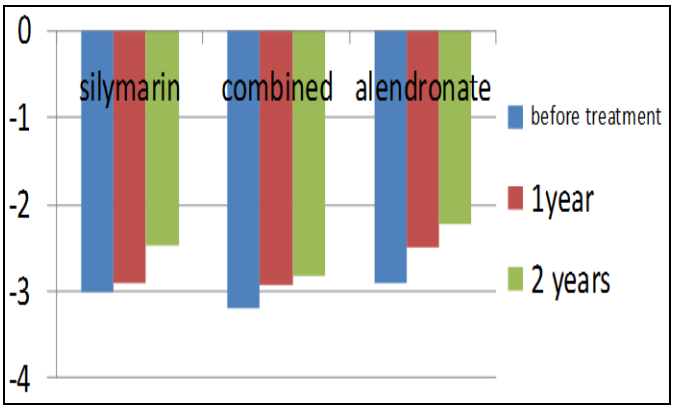

FIG.2: CHANGES IN T-SCORES DURING THE COURSE OF TREATMENT IN DIFFERENT PATIENT GROUPS AS REGARDS FEMUR BMD.

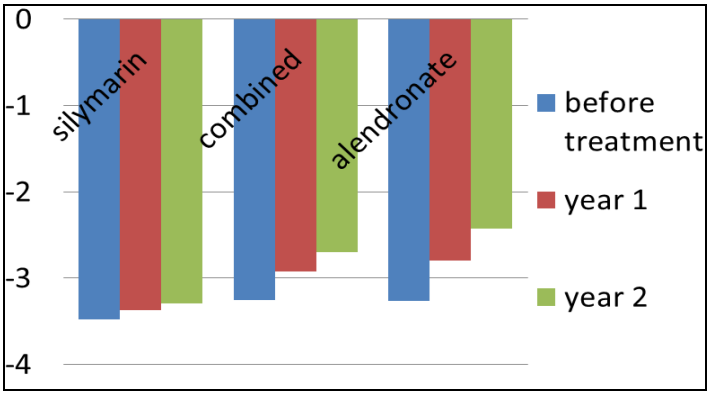

FIG. 3: CHANGES IN T-SCORES DURING THE COURSE OF TREATMENT IN DIFFERENT PATIENT GROUPS AS REGARDS WRIST BMD.

Number of patients affected by side effects in the silymarin group and combined therapy group were less than in alendronate group. In all occurrences of side effects did not lead to discontinuation of therapy therefore not affecting the final results as shown in **Table 6**.

TABLE 6: NUMBER OF PATIENTS AFFECTED BY SIDE EFFECTS IN EACH GROUP

Number of patients / Side effect	Group 1 (Alendronate)	Group 2 (Silymarin)	Group 3 (Combined)	P value
heartburn	8		5	0.070 non-significant
Gastrointestinal disturbance	2	3	1	0.557 non-significant
Oesophageal regurgitation	3			0.060 non-significant
diarrhea	1		2	0.375 non-significant
constipation	1		1	0.596 non-significant
urticaria		2	4	0.134 non-significant
headache			1	0.386 non-significant
Nausea and dizziness		2		0.127 non-significant

DISCUSSION: Numerous studies have shown that silymarin could be considered as a promising pharmacological agent as antiosteoporotic and selective estrogen receptor modulator [7, 14, 15] so this was taken as a the base of the present study. Our study is considered to be the first study done on human being.

The present study showed that patients treated with silymarin showed improvement in the mean T-scores of spine and femur and wrist yet this improvement was significantly less than in patients treated with alendronate or combined therapy (p_{spine} =0.000, p_{femur} =0.000 p_{wrist}=0.033).

Most probably the effect of silymarin on bone is due to its estrogenic effect which has been studied before on ovariectomzed rats in several studies demonstrating the estrogenic effect of silymarin, where El Shitany et al reported the estrogenic effects of silymarin on bone and various body organs in an ovariectomized (OVX) model of postmenopausal bone loss [14]. Results of this study showed that animals administered silymarin had significantly higher uterine weights compared to the OVX rats. This effect was; however, 6.48 times lower in magnitude compared to the effects of ethinylestradiol (EE). Significant increases of uterine weight and endometrial height, as well as hypertrophy of luminal epithelium, have been established as reliable indexes of estrogenic effects [16].

Hence, it could be suggested that silymarin influenced the actions of estrogen or its receptor in the uterus [14]. In addition EL Shitany study demonstrated clear antiosteoporotic effects of silymarin on bone structure as evident by improved trabecula thickness of the femur. In the same concern Sonnenbichler et al reported that silymarin exerted estrogen-like effects on the metaphysis of the femur of OVX rats**.** This study presented an overview of the many estrogenic effects of silymarin in OVX rats. Silymarin significantly prevents the bone loss in rats induced by OVX with mild proliferative effects in uterus [17].

Intensive attention has been paid to flavonoids displaying estrogenic effects (non-steroidal estrogens, phytoestrogens). Similarity of their chemical structure with that of estradiol allows them to bind to and activate estrogen receptors of mammalian target cells. Because of their low binding affinity, they are classified as 'weak estrogens' with a biological activity on the order of 10^{-2} to 10^{-5} that of 17-estradiol [15]. Kummer et al also reported a significant decrease in the intensity of immune staining for estrogenic receptor in uterine epithelial cells was observed both in the groups treated with silymarin and in the positive control groups treated with estradiol. These results indicate that the uterotrophic effects of daily doses of 25 to 50mg of silymarin administered for 30 days were weaker than in the positive control group treated by estradiol and therefore estrogenic effect of silymarin estimated approximately at 10000 to 25000 times lower than that of estradiol [15].

In the study by Jung-Lye et al which showed other mechanisms by which silymarin rich in milk thistle

extract (MTE) can enhance the bone mineral density and bone mineral content which is diminished in ovariectomized mice. In this study, silymarin-rich MTE and silibinin inhibited RANKL-induced bone-degrading activity of osteoclasts. In addition, the bone-forming ALP activity of osteoblasts was also enhanced by MTE. Therefore, MTE may be a therapeutic agent promoting matrix mineralization and antagonizing bone loss. These findings revealed that silibinin rich in MTE as glycoside may prevent postmenopausal osteoporosis due to estrogen deficiency through dampening osteoclastogenesis [18].

Concerning the Alendronate treated group, the present study results are in agreement with Lwamoto et al which indicates that alendronate has been shown to be especially efficacious for the prevention of non-vertebral fractures. The rate of reduction of vertebral fractures following alendronate, was 48%, and the respective rate of non-vertebral fractures was 49% [19]. A meta-analyses conducted by Papapoulos et al demonstrated that the rate of reduction of hip fractures following alendronate treatment in postmenopausal women with osteoporosis was 55%.

According to a report by Rodan et al bisphosphonates normalize the bone turnover rate within weeks of the start of therapy. The reduction in the rate of bone turnover is associated with increased bone mineral density (BMD), more homogeneous mineralization, and reduced fracture risk [20]**.** The reduction in bone turnover and drug retention in the skeleton should be considered during the long term use of bisphosphonates [21].

In the same concern a single masked study by Shiraki et al reported the effects of alendronate treatment at doses of 2.5 and 10 mg daily; lumbar spine BMD increases of approximately 3%were observed among postmenopausal women without osteoporosis at 36 weeks, relative to baseline [22]. Also the study of Gonnelli et al demonstrated a significant increase in BMD lumbar spine was found in the alendronate treated group, estimated at 3.7% after 1 year and 5% after 2 years.

However, increments in bone mass in patients treated with alendronate are variable; in fact, skeletal responses vary at different sites, with a greater response noted in the lumbar spine rather than in the distal forearm or femoral neck, perhaps due to varying rates of bone remodeling [23]. In the study by Henry et al they also found that the vast majority of women who received alendronate had increases in bone mineral density during the 10-year study. For example, 89 percent of women who took the 10-mg dose daily had an increase (as indicated by a change greater than 0) in bone mineral density at the total hip [24]**.**

The study of Dennis et al confirm the safety of alendronate for up to 10 years including no increased fracture risk with long-term alendronate use [25].

As for the Alendronate and Combined therapy group, they both showed improvement in mean T-scores of patients with fewer side effects in combined therapy group, yet superior improvement was noticed in the Alendronate group. To properly asses the synergestic effect of Silymarin with Alendronate further comparison between group receiving 35 mg Alendronate only and combined therapy group receiving 35 mg Alendronate and 140 mg Silymarin is necessary.

Concerning the combined therapy group the results of the present study could be supported by the study of Kim et al on ovariectomized female mice as a model for postmenopausal osteopenia which found that milk thistle extract (MTE) promoted bone-forming activity of osteoblasts and inhibited bone-degrading activity of osteoclasts, which was attributed to osteoprotective effects of silibinin, major constituent of MTE. Pharmacological synergy between MTE and isoflavone-containing soy bean extract (SBE) offered advantages in the treatment of osteoporosis by using lower individual doses. The study by Kim et al found that the combination of low-dose MTE and isoflavone showed a synergic effect on osteogenic and osteoprotective activity of osteoblasts and osteoclasts [26]. It is also well documented that alendronate 35 mg once weekly has a positive effect on improvement of bone mineral density

values in patients with postmenopausal osteoporosis [27].

CONCLUSION: In conclusion this is the first study to be done on postmenopausal females in order to evaluate the clinical outcome of combination therapy of silymarin and alendronate in treatment of postmenopausal osteoporosis compared to the monotherapy of each.

Combining both Silymarin and alendronate therapy yielded better results than treatment with Silymarin alone yet these results do not conclude the synergistic effect of the combination as previous studies have shown improvement of bone mineral density in patients receiving 35 mg weekly dose of alendronate [27]. To reach a conclusion that silymarin alone is efficient drug to treat postmenopausal osteoporosis requires further studies with longer duration, dose assessment and larger patient groups.

ACKNOWLEDGEMENT: We are thankful for the facilities provided at the orthopaedic outpatient department of Qasr Al-Aini hospital, Cairo, Egypt, for carrying out our study.

REFERENCES:

1. Solomon L, Warwick D. Apley's system of orthopaedics 2001; 8: 115.
2. Bennett PN, Brown MJ. Clinical Pharmacology 10th edition 2008; 667-668.
3. Lambrinoudaki I., Botsis D. Bisphosphonates, Annals of the New York Academy of Science 2006; 1092: 403-407.
4. Kren V, Walterova D. Silybin and Silymarin - New effects and applications Biomed Papers 2005; 149: 29-41.
5. Chu SC, Chiou HL, Chen PN, Yang SF, Hsieh YS. Silybinin inhibits the invasion of human lung cancer cells via decreased productions of urokinase-plasminogen activator and matrix metalloproteinase-2. Mol Carcinog 2004; 40: 143-149.
6. Soto C, Mena R, Luna J, Cerbon M, Larrieta E, Vital P. Silymarin induces recovery of pancreatic function after alloxan damage in rats. Life Sci 2004; 75: 2167-2180
7. Gholamreza Karimi et al. Siymarin a promising pharmacological agent, antiosteoporotic and selective estrogen receptor modulator. Iran J Basic Med Sci 2011; 14: 316.
8. Gharagozloo M, Velardi E, Bruscoli S, Agostini M, Di Sante M, Donato V, et al. Silymarin suppress CD4+T cell activation and proliferation: Effects on NFk-B Activity and IL-2 production. Pharmacol Res (2010); 61: 405-409.
9. Psotova J, Chlopcikova S, Miketova P, Hrbac J, Simanek V. Chemoprotective effect of plant phenolics against anthracycline-induced toxicity on rat cardiomyocytes. Part 3. Apigenin, baicalelin, kaempherol, luteolin and quercetin. Phytother Res 2004; 18:516-521.
10. Kiruthiga P, Pandian SK, Devi KP. Silymarin protects PBMC against induced toxicity by replenishing redox status and modulating glutathione metabolizimg enzymes-an in vitro study. Toxicol Appl Pharmacol 2010; 247: 116-128.
11. Nadrash TA, Plushner SL, Delate T. Clinical pharmacists' role in improving osteoporosis treatment rates among elderly patients with untreated atraumatic fractures. Ann Pharmacother 2008; 42: 334-340.
12. Karen von Koeckritz. Overview of Bisphosphonates and Osteoporosis 2012;1-17
13. 3. Rana P, Agarwal S, Agarwal R. Prostate cancer chemoprevention by silybinin: bench to bedside. Mol Carcinog 2006; 45: 436-442
14. El-Shitany NA, Hegazy S, El-Desoky K. Evidences for antiosteoporotic and selective estrogen receptor modulator activity of silymarin compared with ethinylestradiol in ovariectomized rats. Phytomedicine 2010; 17: 116-125.
15. Kummer V, Maskova J, Canderle, J, Zraly Z, Machala M. Estrogenic effect of silymarin in ovariectomized rats. Vet. Med. Czech 2001; 46: 17-23.
16. Tinwell H, Soames AR, Foster JR, Ashby J. Estradiol-type activity of coumestrol in mature and immature ovariectomized rat uterotrophic assays. Environ. Health Prespect 2000; 108: 631-634.
17. Sonnenbichler J, Scalera F, Sonnenbichler I, Weyhenmeyer R. Specific binding of a flavonolignane derivative to an estradiol receptor. Prog. Clin. Biol. Res.1999; 280: 369-374.
18. Jung LK, Yun HK, Min K, Ju HG, Seoung JH, Young HK. Antiosteoclastic activity of milk thistle extract after ovariectomy to suppress estrogen deficiency-induced osteoporosis. Hindawi Publishing Corporation. Biomed Research International 2013; 2-9.
Wahren LE, Hosking D, Hochberg MC. Putting evidence-based medicine into clinical practice: comparing anti- resorptive agents for the treatment of osteoporosis. Curr Med Res Opin 2004; 20: 525-31.
19. Rodan G, Reszka A, Golub E. Bone safety of long term bisphosphonate treatment. Curr Med Res Opin 2004; 20: 1291-300.
20. Lwamoto J, Takeda T, Sato Y. Efficacy and safety of alendronate and risedronate for postmenopausal osteoporosis. Current Medical Research and Opinion 2006; 22: 919-928.
21. Shiraki M, Kushida K, Fukunaga M. A double-masked multicenter comparative study between alendronate and alfacalcidol in Japanese patients with osteoporosis. Osteoporosis Int 2000; 10: 183-92.
22. Gonnelli S, Cepollaro C, Pondrelli C, Martini S, Montagnani A, Monaco R, Gennari C. Bone turnover and the response to alendronate treatment in postmenopausal osteoporosis. Calcif Tissue Int 1999; 65: 359-364.
23. Henry G, Hosking D, Devogelaer JP, Tucci JR, Ronald D, Tonino R. Ten years experience with alendronate for

osteoporosis in postmenopausal women. The New England Journal of Medicine 2004; 350: 1189-99.
24. Dennis M, Ann V, Kristine E, Jane A, Levis S, Sara A, Satterfield S. Effects of continuing or stopping alendronate after 5 years of treatment. American Medical Associatiom 2006; 296: 2934-2936.
25. Kim JL, Kang SW, Kang MK. Osteoblastogenesis and osteoprotection enhanced by flavonolignan silibinin in osteoblasts and osteoclasts. Journal of Cellular Biochemistry 2012; 113: 247-259.
26. Marjorie M, Gilchrist N, Henry G, Davie M, Tobias J. Therapeutic equivalence of alendronate 35 mg once weely and 5 mg daily in prevention of postmenopausal osteoporosis. Obstetrics and Gynecology 2013; 101: 711-721.

How to cite this article:
El-Hamamsy MH, Eltoukhy HG and Hasanein MM: A Pilot Study to Assess the Efficacy and Side Effects of Silymarin Alone and in Combination with Alendronate in Treatment of Postmenopausal Osteoporosis. Int J Pharm Sci Res 2016; 7(3): 1012-20.doi: 10.13040/IJPSR.0975-8232.7(3).1012-20.