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Health Needs of Elderly People at Primary Health Care Centers in Antalya, Turkey ..... page 4

From the Editor

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This issue has papers from basic research to community care. It is rich and variable as usual and reflecting on medical development in the Region.

Kanevetçi,, Z et al, looked at the Health Needs of Elderly at PHC Centers. They did a cross-sectional study that included 438 participants attending PHC centers and 1 outpatient clinic of a private hospital. The "10 Minute Comprehensive Screening" Tool of "WHO-Age Friendly PHC Toolkit" was used. The authors concluded that the "WHO-Age Friendly PHC Toolkit" is an important tool to detect unmet health needs of elderly people in community.

Mirhosseini, F.S et al did a study to determine the effectiveness of self-regulating learning strategies on motivation, self-efficacy and academic performance of fifth grade female students in science lessons. To measure the variables were used the Harter's Educational Motivation Questionnaire (1981) and the academic self-efficacy questionnaire (Mcilroy & Bunting (2001)). The results of the study showed that self-regulating learning strategies have a significant effect on students' motivation and academic self-efficacy ($p < 0.05$). The academic performance of students in the sciences increased significantly.

Zoriasatein, M et al, evaluated antimicrobial properties of derivative peptide of Naja naja snake's venom. The authors stressed that few studies have been done to analyze antibacterial properties and purification of snake venoms. Results of this analysis were compared to effects of 2 antibiotics (Ciprofloxacin and gentamycin). Results showed that the peptide derived from Naja snakes' venom has an antibacterial effect on gram-positive and gram-negative bacteria.

Helvaci, M.R et al, did a series of consecutive patients looking into the use of Acarbose in metabolic syndrome. The study included 451 patients, and 81.8% of them were overweight or obese, 71.3% of them had white coat hypertension or hypertension, 57.2% of them had impaired glucose tolerance or diabetes mellitus, and 71.1% of them had dyslipidemia. The authors concluded that the use of acarbose after the age of 50 years, should be initiated in patients with excess weight after the age of 50 years. Shalchi K.A investigated the effect of mind concentration / relaxation of the body and soul (recovery) on the sport students. The sample included 21 athletes who were selected through availability and voluntary sampling method. The results of covariance analysis showed that the effect of mind concentration / relaxation of body and soul (recovery) on sport students were significant.

Two papers dealt with colon cancer. Colon cancer is the fourth cause of mortality at the world and annually 1.2 million people with the disease are being diagnosed. About 8% of overall mortality rate is associated with colon cancer. Colon cancer has considerably increased in Iran over the last 3 decades and it is the second most common cancer in Iran according to the annual report of National Cancer Institute of Iran. Tezerji, S et al, analysed the effect of resveratrol and quercetin separately and together on Wnt Signalling path regulators, tumour differentiation, dietary intake and weight changes in rat's empirical colon cancer. Sarihi, S et al, looked at the Effect of quercetin on induction of apoptosis and cell proliferation in experimental rat colon carcinoma.

Zohre, M et al, attempted to determine the relationship between social isolation and the quality of sleep of older adults living in bam-based elderly care centers. The authors concluded that social isolation is one of the main factors effective on the quality of sleep of the older adults. Nurses and cares providers to the older adults are required to prepare the ground for improving social interactions. Increase in the quality of sleep facilitates social interactions in the older adults.

Saatlou. M.E et al, investigated the relationship between personality characteristics, locus of control, and self-esteem of nursing and midwifery students of Kashan University of Medical University in 2016. The results indicated that there is a significant and negative relationship between extraversion and locus of control while 54.9% of the variance of students' internal locus of control can be explained through their extraverted personality. A significant relationship was found between introversion and locus of control as well as between introversion and self-esteem. In addition, there was a positive and significant relationship between extraversion and self-esteem while 47% of the variance of students' self-esteem can be explained through their extraverted personality.

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Health Needs of Elderly People at Primary Health Care Centers in Antalya, Turkey

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Abstract

Background: Elderly Friendly Primary Health Care Centers is a World Health Health Organisation (WHO) sponsored initiative to support low resourced primary health care (PHC) organisations for the provision of high quality care to suffering people with disability, frailty and chronic conditions. The aim of this study was to evaluate health needs of patients > 60, who were attending primary health care centers in Antalya, Turkey.

Methods: This cross-sectional study included 438 participants attending PHC centers and 1 outpatient clinic of a private hospital. Patients > 60, without an acute and psychiatric condition or terminal condition, speaking Turkish, and voluteers were included in this study. The "10 Minute Comprehensive Screening" Tool of "WHO-Age Friendly PHC Toolkit" was used. Ten subgroups of the 10 Minute Comprehensive Screening were identified for the scoring process. The data of this study was analysed with descriptive, Chi-Square, T Test and Anova statistics. The level of significance was set to $p< 0.05$.

Results: Participants were 69.4+/-6.06 (61-94) years old. Different subdomains of the "10 minute comprehensive screening" tool revealed that health problems (cognition, urinary incontinence, affective symptoms, mobility, fall risk, malnutrition, hearing impairement, and visual impairment) in participants were frequent and cognitive scores, IADL mobility, total mobility and hearing impairment worsened with increasing age ($p<0.05$). Female participants suffered more urinary incontinence, depressive symptoms, fall proneess, and visual impairment; and male participants more hearing impairment ($p<0.05$).

Discussion: The "WHO-Age Friendly PHC Toolkit" is an important tool to detect unmet health needs of elderly people in the community. The determination of these geriatric problems will help elderly patients and their caregivers/relatives to seek further support from the health system. Family physicians in primary health care and if needed secondary care physicians, will certainly welcome these pre-evaluated patients with a certain management focus.

Key words: Family Practice, Primary Health Care, Geriatric Assessment, Screening, Prevention, Frailty, WHO, Turkey

Introduction

Elderly Friendly Primary Health Care Centers is a World Health Health Organisation (WHO) sponsored initiative to support low resourced primary health care (PHC) organisations for the provision of high quality care to people suffering with disability, frailty and chronic conditions [1,2]. Health authorities of various countries have well accepted the need for equal access to clinical, evidence-based, socially acceptable, and sustainable PHC services. The concept of active aging has been well addressed in the last years and an implementation to PHC services is urgently recommended. At least preparedness to two most frequent chronic conditions (DM, HT) and four geriatric giants (dementia, depression, falls, and urinary incontinence) have been called for action [3].

Periodic evaluation of aging people could contribute to the active aging efforts. The evaluation of functional abilities, psychological status, social parameters and frequently observed conditions of the elderly should be performed with a patient-centred effort. Since PHC facilities are commonly low resourced settings with a heavy workload and insufficient number of staff, pragmatic approaches are needed to address the needs of aging people. By screening and case-finding strategies preventive services, health risk estiamtes and counseling services could be delivered and frequent health problems managed in the PHC setting. Any progression of the condition and need for further evaluation should be referred for consultation to appropriate specialists [4]. No study has addressed this issue by using the 10 minute screening instrument of the WHO Elderly Friendly Primary Health Care Toolkit [3,5].
The aim of this study was to evaluate health needs of patients > 60, who were attending primary health care centers in Antalya, Turkey.

Material and Methods

The data of this study originated from a specialisation thesis in family medicine entitled "The Pilot Implementation of World Health Organisation Age-Friendly Primary Health Care Center Toolkit in Antalya" [6], which was defended at Akdeniz University, Faculty of Medicine in 2008. The data originally covered the range of people between 60-94 years, the "10 Minute Comprehensive Screening" Tool, SF-36 and EUROPEP questionnaires. To provide a better distribution of the dataset, in this study participants between 61-94 years were considered.

This cross-sectional study was performed between 01.06.2007 to 06.12.2007. First the translated version of "WHO-Age Friendly PHC Toolkit" was piloted in a small sample. In July 2007 this study was performed in a larger sample covering 10 PHC centers (≥ 65 population >6%) and 1 outpatient clinic of a private hospital. Patients ≥ 60, without an acute and psychiatric condition or terminal condition, speaking Turkish and volunteers were included in this study. The "10 Minute Comprehensive Screening" Tool of "WHO-Age Friendly PHC Toolkit" was used to screen elderly people attending the PHC centers [3].

The "10 Minute Comprehensive Screening" Tool: This screening tool has 3 sections. The first section comprises the name, age and gender of the patient. The second section includes questions on cognitive status (first 3-Item Test and second 3-Item Test) (3-Item Test for the 1st minute PPV =0.60 and NPV=0.92) [7,8], urinary incontinence (positive answers to both questions revealed a PPV=0.86 and NPV=0.96) [7,8], depressive symptoms (a positive answer revealed a PPV=0.70 and NPV=0.91) [7,8], mobility (Positive response to all 6 items had a PPV=0.88 and NPV=0.77) [7,8] and falls (Timed Stand-Up and Walk Test has a sensitivity of 0.88 and specificity of 0.94. The test of this study is a modification of this test) [9,10]. Additional questions and tests in the third section evaluated for nutritional status (loss of 4.5 kg or <45 kg had a sensitivity of 65-70 and spesifity of 87-88) [7,8]; hearing test (Whisper Test: sensitivity 0.80-1.00 and specificity 0.82-0.89) [7,8] and vision test (Screening Question and Snellen Test: PPV=0.75 and NPV=0.89) [3,7,8] (Figure 1). The internal reliability Cronbach alpha was 0.67 (10 subgroups: Cognitive Score, Urinary Incontinence, Depressive Symptom, IADL Score, ADL Score, Total Mobility Score, Falls Score, Nutrition, Hearing, Vision Score) [5].

Scoring of the "10 Minute Comprehensive Screening" Tool: 10 subgroups have been identified for the scoring process [3,7]:

Cognitive Score: The recall of all three items were scored with 0 points and failure to recall 1 points. The summation of the points of the first and second cognitive tests scores (3-item test) revealed the cognitive score. Patients with a score ≥ 1 points were referred for further evaluation.

Urinary Incontinence Score: "Yes" answer revealed 1 point and "no" answer 0 point to the questions "In the last year have you ever lost your urine and gotten wet?" and "Have you lost urine over the past week?". Patients with a score of 2 points were referred for further evaluation.

Depressive Symptom: A "yes" answer to the question "Do you often feel sad or depressed?" were scored with 1 point and were a reason for further evaluation.

Mobility: Four items comprised the IADL Score (Instrumental Activities of Daily Living) and two the ADL (Activities of Daily Living). Each "yes" answer was scored 1 and "no" answer 2 points. The IADL Mobility Score (min-max=4-8 points), ADL Mobility Score (min-max=2-4 points) and Total Mobility Score (IADL Mobility Score+ ADL Mobility Score; min-max=6-12 points) was calculated by summing up all appropriate item scores. Participants who had at least one deficit in the mobility scores were referred for further evaluation.

Fall Score: Patients giving a positive answer to "Have you fallen 2 or more tims in the past 12 months?" were directly referred for further evaluation and scored with 6 points. A negative answer was the reason for the chair test (Rise from the chair, walk around it without holding on). Positive

performance was scored with 1 point and negative with 2 points. Positive performers were evaluated for steadiness (1 point) and unsteadiness (2 points). Summing up three items and substraction of 3 points revealed the fall score (min-max=0-3).

Nutrition: Answers to the question "Have you noticed a change in your weight over the past 6 months?" were scored with 2 points for "increased", 3 points for "decreased" and 1 point for unchanged. The actual body weight was measured and a body weight below 45 kg or a change of body weight during the last 6 months was a reason for referral.

Hearing Test: The whisper test was applied (Standing behind a person and asking the person to repeat after you - 6, 1, 9; softly, then in normal voice)" and participants with hearing problems were referred for further evaluation.

Vision Score: Positive answers received 1 point (negative response = 0 point) to the question "Do you have difficulty reading or doing any of your daily activities because of your eyesight?" and were examined with SNELLEN eye chart test (without glasses & then with glasses). Vision problems revealed 1 point (normal examination 0 point). Vision score was calculated by summing up both and a vision score of 2 points (min-max=0-2).

Age groups: The variable "age" was grouped into subgroups 61-64, 65-69, 70-74 and ≥75. The data of this study was analysed with descriptive, Chi-Square, T Test and Anova statistics. The level of significance was set to $p<0.05$.

Results

The age of participants (n=438) was 69.4+/-6.06 (61-94). The distribution of age subgroups and genders are shown in Table 1. Positive screening results of the "10 minute comprehensive screening" tool are shown in Table 2.

Table 1: The distribution of age subgroups and gender

	n	%
Age		
61 – 64	106	24.2
65 – 69	133	30.4
70 – 74	116	26.5
75 +	83	18.9
Total	**438**	**100**
Gender		
Male	223	50.9
Female	215	48.1
Total	**438**	**100**

Comparing the changes of different subdomains of the "10 minute comprehensive screening" tool with different variables revealed the following results: Cognitive, IADL mobility, Total Mobility and hearing scores worsened with increase of aging ($p<0.01$). Urinary incontinence, depressive symptoms, fall proneness and vision problems were more frequent in women ($p<0.01$); and hearing problems in males ($p<0.01$). IADL and Total Mobility scores and hearing test was worse in participants with lower cognitive test score ($p<0.01$). Urinary incontinence, vision problems and fall risk was more frequent in patients with depressive symptoms ($p<0.01$). IADL mobility was worse in participants with cognitive, urinary incontinence and hearing problems ($p<0.01$). ADL Mobility was worse with vision problems ($p<0.05$). Total Mobility Score was decreased with cognitive, risk of falls and hearing problems ($p<0.01$). Higher risk of falls was increased in women, and urinary incontinence, depressive symptoms, lower IADL Mobility, lower ADL Mobility, lower Total Mobility, body weight decrease, hearing problems, vision problems, in women ($p<0.01$). More vision problems were observed in participants with body weight loss during the last 6 months ($p<0.01$). Cognitive problems, lower IADL Mobility, lower Total Mobility and vision problems were found in participants with hearing problems ($p<0.01$). Older participants had more frequent hearing problems ($p<0.01$). Urinary incontinence, depressive symptoms, lower ADL Mobility, loss of body weight and hearing problems were more frequent in participants with vision loss ($p<0.01$).

Discussion

This study revealed a worsening of the three-item recall test and an increased frequency of undiscovered health problems (cognition, urinary incontinence, affective symptoms, mobility, fall risk, malnutrition, hearing impairment, and visual impairment in participants. Cognitive scores, IADL mobility, total mobility and hearing impairment worsened with increasing age. Female participants suffered more urinary incontinence, depressive symptoms, fall proneness, and visual impairment; and male participants more hearing impairment.

Cognitive capacity declines with increasing age [11] and saving cognitive capabilities are needed to prevent handicaps and dependency [12]. Our findings are smillar to those findings. The change of failing to achieve the three-item recall tests ranged from 5.5 to 53.2% within one minute. Delay in recall is an important symptom for early dementia or mild cognitive impairment [13]. Single domain tests like the three-item recall test is accepted as an efficient method for screening [14]. The prevalence according to a single domain test has been found at 10.6% (sensitivity 68.5% and specifity 85.9%) [13].

The screen for urinary incontinence in women revealed 28.5 % positivity. This conforms to the prevalence of urinary incontinence in women in different countries, which is estimated to be between 5-69% [15]. Participants (14.4%) screened positive for depressive symptoms. Depression is frequently observed in elderly people and the prevalence in the elderly varies between 7-49 % [16,17]. Patients with depressive symptoms suffered more urinary incontinence, visual impairment and falls risk. The knowledge that

Table 2. Positive screening results of the "10 minute comprehensive screening" tool

Domain		Positive Results; n (%)
Cognitive		
	1. Three-Item Recall (1st)	24 (5.5)
	2. Three-Item Recall (2nd)	233 (53.8) (missing; n=5, %1.1)
	Memory Score (>0 score)	233 (53.8) (missing; n=5, %1.1)
Urinary Incontinence		
	1. In the last year have you ever lost your urine and gotten wet?	120 (27.4)
	2. Have you lost urine over the past week?	37 (28.5) (missing; n=309, %71)
	Urinary Incontinence Score (>1 score)	37 (28.5) (missing; n=309, %71)
Depression		
	1. Do you often feel sad or depressed?	63 (14.4) (missing; n=1, %0.2)
Mobility-IADL	1. Are you able to Run/fast walk to catch the bus?	211 (48.2) (No)
	2. Are you able to do heavy work around the house, like washing windows, walls or floors?	237 (54.1) (No)
	3. Are you able to go shopping for groceries or clothes?	56 (12.8) (No)
	4. Are you able to get to places out of walking distance? (drive, take a bus)	58 (13.3) (No) (missing; n=1, %0.2)
	Mobility-IADL Score	247 (61.2) (at least one deficit)
Mobility-ADL	1. Are you able to bathe, either in a tub bath or shower?	5 (1.1)
	2. Are you able to dress, like putting on a shirt, buttoning and zipping, or putting on shoes?	5 (1.1) (missing; n=1, %0.2)
	Mobility-ADL Score	8 (1.9) (at least one deficit) (missing; n=1, %0.2)
	Total Mobility Score	267 (61.2) (at least one deficit) (missing; n=2, %0.5)
Falls		
	1. Have you fallen 2 or more times in the past 12 months?	42 (9.6) (missing; n=1, %0.2)
	2. Rise from the chair, walk around it without holding on. Able to do:	2 (0.5) (missing; n=50, %11.4)
	3. Rise from the chair, walk around it without holding on. Unsteady:	4 (1.3) (missing; n=128, %29.2)
	Fall Score	45 (12.7) (missing; n=86, %19.6)
Nutrition		
	1. Have you noticed a change in your weight over the past 6 months?	159 (27) (missing; n=8, %1.8)
	2. Weight Change	Increase: 53 (12.3) Unchanged: 271 (63.0) Decrease: 106 (24.7)
	3. Body Weight (<45 kg)	1 (0.2)
Hearing		
	1. Stand behind person and ask the person to repeat after you - 6, 1, 9; (softly then in normal voice)	134 (30.4) (missing; n=4, %0.9) (Needs Audiogram)
Vision		
	1. Do you have difficulty reading or doing any of your daily activities because of your eyesight?(even with wearing glasses)	207 (49.9) (missing; n=23, % 5.3) (Needs Snellen Exam)
	2. If positive screen, if available, ask to complete SNELLEN eye chart (without glasses & then with glasses)	63 (33.3) (missing; n=249, % 56.8) (Needs Eye Exam)
	Vision Score	63 (33.3) (missing; n=249, % 56.8) (Needs Eye Exam)

depression increases morbidity and mortality might support these findings [18]. Similar to our study, depression has been reported higher in women than men [19].

Screening for mobility revealed positivity for IADL in 61.2%, ADL in 1.1%, and total mobility in 61.2%. In a study by Bahat G et al. IADL was found at 64% and ADL 23.4% [20]. Disability and the increase of prevalence with age is well described in older people and is well reported in the literature [21].

Fall risk was positive in 12.7% and more frequent in female participants. The increased risk of fall risks could be explained with the change of gait patterns in aging people [22]. The question on perceived weight change during the last six months revealed 27% positivity. Weight changes are frequently observed in elderly people. In a study, weight increased until 70 years of age and declined in both sexes afterwards [23]. These changes are explained by different factors such as physiological, psychological and social factors [24].

The screen for hearing impairment was positive in 30.4% of participants. Loss of 25 dB and more involves 37 % of older people 61-70 years, 60 % of 71- 80 years, and over 80 % > 85 years [25]. This might have negative effects on functioning and wellbeing in people [18]. Hearing impairment is also increasing with age [26]. Men, such as those in our study, suffer more and have an earlier onset of hearing deficits than women [27].

Visual examination with the Snellen eye chart revealed a positivity of 33.3%. Different levels of frequencies have been detected in older people, but commonly the prevalence of visual impairment is increased [28]. Visual impairment in elderly people is associated with increased risk of falls and cognitive impairment [29]. Visual impairment and risk of falling was more frequent in women. One study made an observation on visual impairment and lower extremity deficits. Shared background factors might cause vision and lower extremity impairment [30].

Conclusion

The aged-friendly primary health care toolkit is an important instrument to detect unmet health needs of elderly people in the community. The ten minute screening instrument contained items, which were previously validated [7]. The definition of these geriatric problems will certainly help elderly patients and their caregivers/relatives to seek further support in the health system. Family physicians in primary health care and if needed secondary care physicians, will certainly welcome thses pre-evaluated patients with a certain management focus.

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Acarbose versus metformin in the treatment of metabolic syndrome

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Abstract

Background: Prevalence of excess weight is increasing after the age of 50 years with a high cost on health in society.

Method: Consecutive patients with excess weight desiring weight loss at and above the age of 50 years were divided into two subgroups according to wishes of patients as to whether they preferred medication or just a diet. Acarbose 100 mg three times daily was initiated in the medication group, orally.

Results: The study included 451 patients, and 81.8% of them were overweight or obese, 71.3% of them had white coat hypertension or hypertension, 57.2% of them had impaired glucose tolerance or diabetes mellitus, and 71.1% of them had dyslipidemia. Initially, 179 patients preferred acarbose. Only 10.6% of patients stopped the acarbose therapy due to excessive flatulence or loose stool. The mean weight loss was 8.3 ± 4.1 kg (0-23) in the acarbose group, whereas it was 0.8 ± 1.3 kg (0-7) in the diet group ($p<0.001$). Although body mass index, low density lipoprotein cholesterol, triglyceride, high density lipoprotein cholesterol, fasting plasma glucose, and systolic and diastolic blood pressure at home decreased with acarbose, significantly ($p<0.001$ for all), none of them decreased with diet, significantly ($p>0.05$ for all).

Conclusion: Due to the high prevalence of excess weight and its consequences after the age of 50 years, acarbose should be initiated in patients with excess weight after the age of 50 years. It should be preferred to metformin due to high prevalence of excessive anorexia induced metformin intolerance in the society.

Key words: Acarbose, metformin, excess weight, metabolic syndrome, chronic endothelial damage, atherosclerosis

Introduction

Due to the prolonged survival of human beings, systemic atherosclerosis may be the major health problem in this century, and its association with some metabolic disorders and smoking and alcohol are collected in the box of metabolic syndrome in the literature (1, 2). The syndrome is characterized by a chronic low-grade inflammatory process on vascular endothelium all over the body (3). The inflammatory process is exaggerated by some factors including aging, physical inactivity, excess weight, smoking, alcohol, chronic infection and inflammation, and cancer (4, 5). The inflammatory process can be slowed down with lifestyle changes, diet, and exercise (6). The syndrome includes some reversible parameters such as physical inactivity, overweight, white coat hypertension (WCH), impaired fasting glucose, impaired glucose tolerance (IGT), hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, smoking, and alcohol for the development of irreversible consequences such as obesity, hypertension (HT), type 2 diabetes mellitus (DM), chronic obstructive pulmonary disease, chronic liver disease, chronic renal disease, peripheral artery disease, coronary heart disease (CHD), and stroke (7-9). The syndrome has become so common all over the world, for example 50 million people in the United States are affected (10). The inflammation induced accelerated atherosclerosis all over the body may be the leading cause of early aging and premature death for both genders all over the world. Physical inactivity induced excess weight may be the major underlying cause of the metabolic syndrome. Excess weight is a disorder characterized by increased mass of adipose tissue. The chronic inflammation inducing endothelial dysfunction probably is the action of excess weight for the increased atherogenicity (11, 12). There are some reports about beneficial effects of acarbose on excess weight and associated disorders in the literature (13, 14). We tried to understand whether or not acarbose has some beneficial effects on excess weight and associated disorders in the present study.

Material and Methods

The study was performed in the Internal Medicine Polyclinic of the Mustafa Kemal University on routine check up patients between March 2007 and July 2011. Consecutive check up of patients with excess weight, desiring weight loss at and above the age of 50 years were taken into the study. They were divided into two subgroups according to wishes of patients as to whether they preferred medication or just a diet. Their medical histories including HT, DM, dyslipidemia, and already used medications were learnt, and a routine check up procedure including fasting plasma glucose (FPG), low density lipoprotein cholesterol (LDL-C), triglyceride, and high density lipoprotein cholesterol (HDL-C) was performed. Patients with devastating illnesses including type 1 DM, malignancies, acute or chronic renal failure, chronic liver disease, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on weight. Body mass index (BMI) of each case was calculated by measurements by the same physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared, and underweight is defined as a BMI of lower than 18.5 kg/m2, normal weight between 18.5-24.9 kg/m2, overweight between 25.0-29.9 kg/m2, and obesity as 30.0 kg/m2 or greater (15). Cases with an overnight FPG level of 126 mg/dL or higher on two occasions were defined as diabetics. An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 110 and 125 mg/dL, and diagnosis of cases with a 2-hour plasma glucose level of 200 mg/dL or greater is DM and between 140-199 mg/dL is IGT (15). Additionally, dyslipidemia is diagnosed when LDL-C is 160 mg/dL or higher and/or triglyceride is 200 mg/dL or higher and/or HDL-C is lower than 40 mg/dL (15). Office blood pressure (OBP) was checked after a 5-minute rest in seated position with a mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2 hours. A 10-day twice daily measurement of blood pressure at home (HBP) was obtained in all cases, even in normotensives in the office due to the risk of masked HT after 10 minutes of education about proper blood pressure (BP) measurement techniques (16). The education included recommendation of upper arm while discouraging wrist and finger devices by using a standard adult cuff with bladder sizes of 12 x 26 cm for arm circumferences up to 33 cm in length and a large adult cuff with bladder sizes of 12 x 40 cm for arm circumferences up to 50 cm in length, and taking a rest at least for a period of 5 minutes in the seated position before measurement. An additional 24-hour ambulatory BP monitoring was not required due to the equal efficacy of the method with HBP measurements to diagnose HT (17). Eventually, HT is defined as a mean HBP of 135/85 mmHg or greater, WCH as an OBP of 140/90 mmHg or greater but mean HBP of lower than 135/85 mmHg, and masked HT as an OBP of lower than 140/90 mmHg but mean HBP of 135/85 mmHg or greater (16). The diet was poor for animal sourced foods but rich for vegetables and fruits divided into four to six small meals and snacks everyday in the diet group. To simplify the diet, only one kind of animal sourced diet with a low amount was permitted daily, and fruits were advised before meals to provide saturation. Additionally, foods that are high for sugars such as pastries, candy bars, pies, and candy were restricted. Acarbose 100 mg (Bayer, Turkey) three times daily was initiated for the medication group, orally, but the total dose was reached in the third week by increasing the dose 100 mg per week just to decrease possible side effects of acarbose. Patients were followed up for a period of six-months with four-week intervals. At the end of this period, the acarbose and diet groups were evaluated for the previous and final BMI, LDL-C, triglyceride, HDL-C, FPG, and systolic and distolic HBP values, separately. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 451 cases at and above the age of 50 years, and just 18.1% of them were normal weight with a mean age of 51.9 years (56.0% females), and none of them was underweight. So 81.8% (369 patients) of cases at and above the age of 50 years were overweight or obese. Beside that 71.3% (322 patients) of them had WCH or HT, 57.2% (258 patients) had IGT or DM, and 71.1% (321 patients) had dyslipidemia (Table 1).

Table 1: Characteristics of the study cases at and above the age of 50 years

Variables	Prevalence (n= 451)
Overweight	43.0%
Obesity	38.8%
WCH*	40.1%
HT†	31.2%
IGT‡	23.2%
DM§	33.9%
Hyperbetalipoproteinemia	34.3%
Hypertriglyceridemia	46.1%
Dyslipidemia	71.1%

*White coat hypertension †Hypertension ‡Impaired glucose tolerance §Diabetes mellitus

Initially, 190 patients with excess weight preferred the diet and 179 patients preferred acarbose therapy alone. Only 19 patients (10.6%) stopped the acarbose therapy due to excessive flatulence or loose stool, and 15 patients (7.8%) stopped the diet for various reasons during the follow up period. Finally, the mean age of acarbose therapy patients was 57.5 years and 68.1% of them were female. Similarly, the mean age of the diet cases was 57.1 years and 65.7% of them were female, again. The mean weight loss was 8.3 ± 4.1 kg (0-23) in the acarbose group, whereas it was 0.8 ± 1.3 kg (0-7) in the diet group ($p<0.001$). Although the mean BMI, LDL-C, triglyceride, HDL-C, FPG, and systolic and diastolic HBP values decreased with the acarbose therapy, significantly ($p<0.001$ for all) (Table 2), none of the above parameters decreased with the diet, significantly ($p>0.05$ for all) (Table 3).

Table 2: Comparison of acarbose group before and after therapy

Mean values	Before acarbose therapy	After acarbose therapy	*p*-value
BMI* (kg/m²)	33.3 ± 5.3 (25.0-45.5)	30.2 ± 4.6 (24.3-44.3)	<0.001
LDL-C† (mg/dL)	139.3 ± 31.2 (95-213)	131.3 ± 27.3 (91-209)	<0.001
Triglyceride (mg/dL)	149.3 ± 47.7 (87-402)	139.7 ± 53.3 (76-353)	<0.001
HDL-C‡ (mg/dL)	51.1 ± 10.7 (25-61)	48.2 ± 10.9 (27-59)	<0.001
FPG§ (mg/dL)	129.4 ± 35.3 (109-247)	114.3 ± 28.4 (101-236)	<0.001
Systolic HBP** (mmHg)	145.7 ± 23.6 (111-185)	138.2 ± 21.3 (113-189)	<0.001
Diastolic HBP (mmHg)	96.5 ± 15.3 (69-130)	91.4 ± 14.1 (71-129)	<0.001

*Body mass index †Low density lipoprotein cholesterol ‡High density lipoprotein cholesterol §Fasting plasma glucose **Home blood pressure

Table 3: Comparison of diet group before and after therapy

Mean values	Before diet therapy	After diet therapy	*p*-value
BMI* (kg/m²)	33.3 ± 3.3 (25.0-44.5)	33.0 ± 3.6 (25.0-44.6)	Ns†
LDL-C‡ (mg/dL)	137.2 ± 22.4 (77-231)	136.3 ± 25.3 (81-211)	Ns
Triglyceride (mg/dL)	151.3 ± 43.3 (89-415)	150.4 ± 41.4 (99-425)	Ns
HDL-C§ (mg/dL)	51.7 ± 10.4 (25-60)	51.8 ± 10.3 (29-57)	Ns
FPG** (mg/dL)	127.3 ± 29.2 (107-306)	126.1 ± 31.5 (106-319)	Ns
Systolic HBP*** (mmHg)	141.1 ± 26.3 (117-189)	140.6 ± 25.6 (119-195)	Ns
Diastolic HBP (mmHg)	95.1 ± 17.2 (76-121)	94.9 ± 15.3 (73-137)	Ns

*Body mass index †Nonsignificant ($p>0.05$) ‡Low density lipoprotein cholesterol §High density lipoprotein cholesterol **Fasting plasma glucose ***Home blood pressure

Discussion

Probably obesity is found among one of the irreversible consequences of the metabolic syndrome since after development of obesity, non-pharmaceutical approaches provide limited success to heal obesity. Excess weight may lead to a chronic low-grade inflammation on vascular endothelium all over the body, and risk of death from all causes including cardiovascular diseases and cancers increases parallel to severity of excess weight in all age groups (18). The chronic low-grade inflammation on vascular endothelium may even cause genetic changes in the cells, and the systemic atherosclerotic process may decrease clearance of malignant cells by the immune system, effectively (19). Similarly, effects of excess weight on BP have shown previously that the prevalence of sustained normotension (NT) was significantly higher in the underweight (80.3%) than the normal weight (64.0%) and overweight cases (31.5%, $p<0.05$ for both) (20), and 52.8% of cases with HT had obesity against 14.5% of cases with sustained NT ($p<0.001$) (21). So the major component of the metabolic syndrome may appear as excess weight, which is probably the main cause of insulin resistance, dyslipidemia, IGT, and WCH by means of a chronic low-grade inflammatory process on vascular endothelium (6). Stopping of weight gain with physical activity or diet, even in the absence of a prominent weight loss, probably results with resolution of many parameters of the syndrome (22, 23). But according to our opinion, limitation of excess weight as an excessive fat tissue in and around the abdomen under the heading of abdominal obesity is meaningless; instead it should be defined as overweight or obesity by means of BMI since adipocytes function as an endocrine organ by producing a variety of cytokines and hormones everywhere in the body (6). The resulting hyperactivities of sympathetic nervous system and renin-angiotensin-aldosterone system are probably associated with the chronic low-grade inflammation on vascular endothelium terminating with insulin resistance and an elevated BP. Similarly, Adult Treatment Panel III reported that although some people are classified as overweight with a larger muscular mass, most of them actually have excessive fat tissue, too (15).

Acarbose, a pseudotetrasaccharide, is a natural microbial product derived from culture broths of Actinoplanes strain SE 50. It is an alpha-glucosidase inhibitor. It binds reversibly, competitively, and in a dose-dependent manner to oligosaccharide binding site of alpha-glucosidase enzymes in the brush border of the small intestinal mucosa. It inhibits glycoamylase, sucrase, maltase, dextranase, and pancreatic alpha-amylase. It has little affinity for isomaltase but it does not have any effect on beta-glucosidases such as lactase. As a result, it delays the intestinal hydrolysis of oligo- and disaccharides by alpha-glucosidases mainly in the upper half of the small intestine. Consequently, the absorption of monosaccharides after a meal is delayed and transport through the mucosal surfaces into the circulation is interrupted. On the other hand, it does not have any direct effect on absorption of glucose. Although the acute effect is seen within a few minutes, its effects can last for 3 to 5 hours. Acarbose should be taken with the first bite of a meal. The suppression of alpha-glucosidases is reversible, although pharmacological activity is reliable and persistent with long-term use. Effects with continued use can be maintained over years. Up to now, acarbose failure has not been reported in the literature. Initial therapy with an alpha-glucosidase inhibitor often results with carbohydrates appearing in the colon, where bacterial fermentation occurs, accounting for the frequency and severity of gastrointestinal adverse effects such as flatulence, loose stool, and abdominal discomfort (24). If started at a low dose and titrated slowly, acarbose tends to cause occasional gastrointestinal side effects that are generally tolerable (25). Long-term treatment with acarbose increases colonic bacterial mass, that of lactobacteria in particular. The finally impaired carbohydrate absorption, increased bacterial carbohydrate fermentation, and fecal acidification mimic effects of lactulose or lactilol in patients with liver cirrhosis and portosystemic encephalopathy. So acarbose has a favourable therapeutic profile for the long-term treatment of patients with type 2 DM and liver cirrhosis. Similarly, observed changes in bacterial flora and decreased stool pH and beta-hydroxybutyrate may be associated with antiproliferative effects on epithelial cells in colon that may potentially decrease the risk of carcinogenesis. Acarbose is poorly absorbed and systemic bioavailability is low. After oral administration, less than 2% of the unchanged drug enters into the circulation, with most of the remaining in the lumen of the gastrointestinal tract. Thus there is no need for dosage adjustment in slight renal insufficiency.

After a high carbohydrate meal, acarbose lowers the postprandial rise in blood glucose by 20% and secondarily FPG by 15% (13). Similarly, it lowers fasting and postprandial insulin levels. The initial improvement in blood glucose with acarbose tends to be modest, but efficacy steadily improves with the long-term use, and is maintained over several years without evidence of decreased effect or treatment failure. The beneficial effects of acarbose on serum lipids were also described with a dose-dependent manner (13), since dietary carbohydrates are key precursors of lipogenesis, and insulin plays a central role for postprandial lipid metabolism. Carbohydrate-induced postprandial triglyceride synthesis is reduced for several hours by acarbose, so acarbose lowers plasma triglyceride levels (13). The same beneficial effect is also seen in non-diabetic patients with hypertriglyceridemia, and acarbose reduced LDL-C significantly, but HDL-C remained as unchanged in hyperinsulinemic and overweight patients with IGT (26). Significantly elevated levels of ursocholic acids in the stool appear to be the additive consequence of a decreased rate of absorption and increased intestinal motility due to the changes of intestinal bacteria. Acarbose may lower serum LDL-C by means of an increased fecal bifido bacteria, fecal biliary acids, and LDL-C uptake by the liver. Acarbose together with insulin therapy was identified to be associated with greater improvement in oxidative stress and inflammation in patients with type 2 DM when compared with those who received insulin therapy alone (27). Similarly, acarbose may improve release of glucagon-like peptide-1, inhibit platelet activation, increase epithelial nitrous oxide synthase activity and nitrous oxide

concentrations, promote weight loss, decrease BP, and eventually prevent endothelial dysfunction (13). So acarbose also prevents CHD and other cardiovascular events in patients with excess weight even in the absence of IGT and DM (28, 29). Although some authors reported that the patient population where acarbose is an appropriate selection is limited (30), according to our clinical observations, acarbose should be considered a first-line antidiabetic agent, and is an effective pharmacological option for preventing diabetes in the prediabetic patients. Based on more than 20 years of clinical use of acarbose, numerous studies have not demonstrated any significant toxicity (14). On the other hand, acarbose has not any effect on nutrient intake and patients' eating habits.

Metformin, a biguanide, is currently being used in more than 90 countries worldwide. It is not metabolized in body and 90% of absorbed drug is eliminated as unchanged in the urine. Plasma protein binding is negligible, so the drug is dialyzable. According to literature, antihyperglycemic effect of metformin is largely caused by inhibition of hepatic gluconeogenesis, increased insulin-mediated glucose disposal, and inhibition of fatty acid oxidation (31). Reduction of intestinal glucose absorption has been postulated as another possible mechanism of action (32). Precise mechanism of intracellular action of metformin remains uncertain. Interestingly, 25.9% of patients stopped the metformin therapy due to excessively lost appetite in the previous study (23). Additionally, 14.1% of patients with overweight or obesity in the metformin group rose either to normal weight or overweight group by weight loss without a diet regimen (23). According to our opinion, the major effect of metformin may be a powerful inhibition of appetite. Similar results indicating the beneficial effects of metformin on the BMI, BP, FPG, and lipids have also been reported (33, 34). Probably the major component of the metabolic syndrome may be excess weight and its consequences which can be prevented by suppression of appetite by means of metformin. So treatment of excess weight with metformin will probably prevent not only the IGT or DM but also most of the other consequences of excess weight. Due to the very low risk of life threatening side effects of metformin, which we have never seen in our clinic before, it can be initiated for the majority of cases with excess weight, but clinicians must be careful above the age of 70 years due to risks of comorbid disorders including chronic renal failure, a tendency to develop sepsis, and debility induced weight loss in elders. Although 25.9% of patients stopped the metformin therapy due to excessive anorexia in the above study (23), only 10.6% of patients stopped the acarbose therapy due to excessive flatulence or loose stool in the present study. So acarbose intolerance is significantly lower than metformin intolerance in the society ($p<0.001$). Eventually, acarbose can be used in a larger patient population than metformin according to our clinical experiences, thus we did not put an upper limit of age to start acarbose therapy for patients in the present study.

As a conclusion, due to the high prevalences of excess weight and its consequences after the age of 50 years, and the detected significant benefits of acarbose in prevention of them, acarbose should be initiated in patients with excess weight after the age of 50 years. It should be preferred against metformin due to the high prevalence of excessive anorexia induced metformin intolerance in society.

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Surveying the relationship between the social isolation and quality of sleep of the older adults in Bam-based Elderly Care Centers in 2017

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Abstract

Background and objective: The number and population ratio of older adults are growing in all countries. Rather than living longer, the main concern of the new century is to increase the quality of life and mental welfare. The quality of life is one of the issues that affects different aspects of physical and psychological life. Social isolation, by definition, is having no-one or access to no-one to ask for help and rely on. It is one of the factors that generally affects mental-physical health of older adults. The present study is an attempt to determine the relationship between social isolation and the quality of sleep of older adults living in Bam-based elderly care centers.

Methodology: An applied study was carried out through descriptive-correlative method. Data gathering method consisted of field and library study. Study population included all older adults living in Bam, Iran in 2017. The sample group was comprised of the older adults living in Sepehr Elderly Care Center who were selected through census method. Research tools included Petersburg Sleep Quality Index and UCLA Social Isolation Scale. The collected data was analyzed using descriptive statistics and Pearson's correlation coefficient in SPSS.

Finding: Totally, 80 older adults including 36 men and 44 women took part in the study. Mean score of social isolation was 48.06±15.7 and the subjects with highest social isolation score were the majority group (43.8%). Mean score of the quality of study was 16.76±8.65 and the subjects with the lowest quality were the majority of the study group (38.8%). There was a significant and inverse relationship between social isolation and the mean score of quality of sleep (r=0.675; p=0.000).

Conclusion: Social isolation is one of the main factors effective on the quality of sleep of the older adults. Nurses and care providers to the older adults are required to prepare the ground for improving social interactions. Increase in the quality of sleep facilitates social interactions in the older adults.

Key words: elderly, social isolation,
sleep depreivation

Introduction

Old age in Europe and the USA is defined based on calendar age. From laws and occupation points of view a senior citizen is an individual older than 65 years old. In another common way, people at the age range 65-75 are called "young-old," 75-85 as "old-old," and older than 85 as "oldest-old" [1]. Thanks to scientific advances, a surge in older adults' population has been witnessed over the past years. By 2030, the older adults' population will growth from 9% to 16% of the population in the world and from 5.6% to 17.5% of the population in Iran [2]. On the other hand, older adults experience a decrease in their capabilities both physically and mentally and they are at higher risk of diseases and mental problems. Physical diseases like heart failure, respiratory problems, osteoporosis, digestive problems, and a variety of brain traumas and mental disorders like anxiety, depression, addiction, sleep problem, and sexual problems are part of the challenges that older adults are faced with [3]. Along with the increase in life expectancy, more attention should be paid to the physical health of older adults with more emphasis on providing proper interventions to meet the emotional needs of older adults.

The necessity of more efficient psychological treatments grows with aging [4]. In addition to physical limitations caused by aging, deterioration of psychological functions is notable. Studies have shown aging intensifies psychological problems and the cognitive failure symptoms [5]. The changes induce deep effects on life and mental health and a flexible personality facilitates adaptation to changes. On the other hand, when the older adult perceives the changes negatively, a decrease in flexibility and adaptability is unavoidable [6]. Sleep problems are of the common problems among the older adult and the reason for many visits to clinics [7]. Lack of adequate sleep and low quality of sleep affects the process of treatment of physical problems and the mental pathological symptoms in older adults. Moreover, there is a vicious circle at work; the treatment process in older adults can be an external factor effective on sleep that attenuates the quality and quantity of sleep through the development of disordered sleep habits [8]. Recent studies on the quality of sleep in older adults have shown that almost one half of the subjects did not have adequate sleep overnight and there were frequent reports of day drowsiness [9]. Some authors find the lack of social support and a sense of being deserted to blame for sleep problems of older adults [4]. Taking into account vulnerability-environmental facilities theory, one of the social variables with a profound effect on the quality of sleep in older adults, and those in elderly care centers in particular, is social interaction. Residents of elderly care centers who suffer from social isolation and loss of warm relationships with family members become more susceptible to a deep sense of loneliness and life meaninglessness. Life in these centers is usually featured with the loss of meaning of life and hope, which results in a persistent sense of isolation and loneliness and further physical-mental problems [3]. Social isolation is defined as receiving no love, help, and attention from the family members and others [10]. Studies to determine quality of sleep of the elderly and the effective factors have reported a direct relationship between sleep disorder and physical activity, flushing, anxiety, relationship with kin, and physical and care factors. Although, the majority of the participating older adults report trivial-moderate sleep disorder, taking into account popularity of sleep drugs, the actual sleep disorder must be worse than what is reported. The results have shown that the quality of sleep of older adults is related to physical, mental-social, and care factors [11]. According to Bastani et al. who surveyed the prevalence of social isolation based on social exclusion in the older adults living in Tehran, the exclusion that was objectively experienced by the subjects led to mental exclusion and social isolation eventually. Another study to determine quality of sleep and the effective factors in the retired teachers living in Kashan-Iran showed that the subjects had better quality of sleep compared with the general population [12]. Taking into account the growing population of older adults in Iran, it is essential to identify the factors effective on the improvement of physical and psychological health of individuals. In general, the negative effects of inadequate support and care provided to older adults and the effects of nurses' characteristics on the health condition and quality of sleep of older adults are mostly neglected in Iranian society. In light of this, a study in this field might be a small step toward removing ambiguities and paying more attention to the growing population of older adults in Iran. On the other hand and recognizing that prevention is better than treatment, finding proper preventive measures for the deteriorating quality of sleep in older adults and solutions to improve social support for them are essential. By devising and promoting recommendations to avoid sleep problems in older adults, the destructive consequences can be avoided. These cannot be realized unless the nurses' attitudes toward the older adults are improved and the effective factors are identified. The question asked in this work is "whether the social isolation of the older adults is related to their quality of sleep?" Thereby, the present study is an attempt to determine the relationship between social isolation and the quality of sleep in older adults living in Bam, Iran in 2017.

Methodology

With regard to the objective, the study is categorized as an applied work with descriptive-correlative design. The relationship between social isolation and the quality of sleep was examined. Study population consisted of older adults living in the elderly care centers located in Bam, Iran in 2017. A sample group was selected from the residents of Sepehr Elderly Care Center through census method (n=80). Inclusion criteria were age >60 years, no history of medical disorders (based on medical file and self-statement), no disabling chronic disease (medical file), 24/7 residence at the center, at least six months' experience of life in the center, no cigarette or alcohol dependence, and consent to participate.

The data gathering tools were a personal information questionnaire (age, gender, education, and marital

status), social isolation scale, and Petersburg's sleep quality index (PSQI).

Social isolation scale was designed by Russel et al. (1978) to survey the objective feelings of an individual about social isolation. Although, the reliability and validity of the questionnaire were acceptable, the designers introduced a new version of the scale by removing some of the weaknesses of the tool. Once more the scale was revised by Russel (1996) and the latest version with 20 statements measures social isolation of the respondent. The questions are designed based on Likert's four-point scale (never = 1, rarely = 2, sometime = 3, and always = 4). The questions 20, 19, 16, 15, 10, 9, 6, 5, and 1 are scored inversely (never = 4, rarely = 3, sometime = 2, and always = 1). Maximum and minimum scores of the scale are 80 and 20 respectively [13]. To interpret the scores, 20 - 39 is considered as low social isolation, 40-60 as moderate social isolation, and 61-80 as high social isolation. Cronbach's alpha for the social isolation scale was calculated by Russel et al. (1995) between 0.94 and 0.89 for adults, students and teachers.

Petersburg's sleep quality index is one of the renowned tools that measures the quality of sleep over the past month. The questionnaire was introduced by Daniel J. Bois (1989). Studies have reported good correlation between the results of the questionnaire and lab tests. The questionnaire is a self-statement tool. It is comprised of 9 questions and since question 5 consists of 10 secondary statements, the total number of statements is 18. The ten secondary statements of question 5 and the questions 6-9 are designed based on Likert's four-point scale (0-3). The questionnaire measures seven sub-scales of the quality of sleep including subjective quality of sleep, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. The scores obtained for each subscale are categorized as normal, trivial problem, moderate problem, and severe problem. The sum of the scores of all sub-scales gives the total score that ranges from 0 to 21 [14]. The total score 0-7 is interpreted as good, 8-14 as moderate, and 15-21 as low. Bios et al. (1989) reported the internal consistency of the tool using Cronbach's alpha equal to 0.83.

To initiate the study, the author secured a letter of recommendation from the Islamic Azad University-Isfahan (Khorasgan) addressed to the head of Sepehr Elderly Care Center. The subjects expressed their consent orally and in writing. Eighty older adults living in the center were selected through census method in Autumn 2017. Immediately after selecting the participants, they were interviewed and the tools were filled out for each one. Each participant was given 10-20 minutes to fill out the tools and they were recommended to do so by taking into account their mental condition and personality. In addition, the participants were ensured about confidentiality of their information and the subjects were informed about the date of administering the questionnaire one day in advance. In the case that any of the respondents was not ready to fill out the questionnaire, the process for that participants was postponed to the next day.

Descriptive statistical tools like mean and standard deviations in SPSS were used to describe and summarize the data. To test the hypotheses, MANOVA and Pearson's correlation coefficient were used.

Findings

The majority (37.5%) of the respondents had high school diploma and 16.3% had associates' degree. In addition, the majority (62.5%) were married and 18.8% were widow(er). The number of female participants was higher than that of male participants and mean age of the subjects was 86.37 years. Table I lists the demographics of the participants.

In terms of social isolation, the findings showed that the majority (43.8%) suffered from high social isolation. Mean score of social isolation of the subjects was 48.06±15.7; this figure is higher than UCLA social isolation score. In addition, the majority (38.8) had low quality of sleep and mean score of quality of sleep was 16.76±8.65. This score is higher than global means score of PSQI. Table 2 lists the data about social isolation and quality of sleep of the subjects.

As listed in the table above, 22.28% had the highest means score of sleep quality, which means the lowest quality of sleep; this group also had the highest score of social isolation. Moreover, 5.83% had the lowest score of sleep deprivation, which means the highest quality of sleep; this group reported low social isolation. Pearson correlation test was significant, which means there was an inverse relationship between social isolation and the mean score of sleep quality (P=0.000, r=-0.679).

Discussion

There was an inverse relationship between social isolation and quality of sleep of the subjects; so that the higher social isolation scores were observed in the subjects with the lower quality of sleep. That is, the elderly with high social isolation had a lower quality of sleep. While no similar study was found in this area, Asgharpour and Eibpoush (2011) reported almost consistent results in their study titled "Determining quality of sleep of the older adults living in Kahrizak Care Center and the effective factors." They mentioned a relationship between quality of sleep and physical activity, flushing, anxiety, relationship with kin, physical/mental factors, and care services.

Given that the older adults are a unique group of society with special needs, providing care and nursing services to them entails specially trained experts with adequate practical and scientific capabilities. Although, providing care to the elderly is the job of a team of geriatric medicine specialists, geriatric psychiatrists, geriatric nurses, physiotherapists, psychologists, work therapists, nutrition specialists, social support experts and the like, the role of the geriatric nurse is unique and of higher importance taking into account the continuous interaction between the nurse and the older adult and the role of nurse as the coordinator of the team. The necessity of tailored health services based on the needs of the target community

Table 1: Demographics of the participants (2017)

Variable		N	%
Education	Junior high school	19	23.8
	Highs school	30	37.5
	Associates' degree	13	16.3
	Bachelors' degree	18	22.5
Marital status	Married	50	62.5
	Widow(er)	15	18.8
	Divorced	15	18.8
Gender	M	36	45.0
	F	44	55.0
Age (year)	60-64	23	28.8
	65-69	20	25.0
	70-7	28	35.0
	75-79	9	11.3

Table 2: Social isolation and mean quality of sleep score of the subjects

Social isolation	N	%	Mean quality of sleep	R	P
Low	12	15	5.83		
Moderate	33	41.3	14.87		
High	35	43.8	22.28	0.679	0.000
Total	80	100	76.16		

and, most importantly, home nursing services to older adults with severe and chronic mental, physical, and social problems is another key issue to be covered by geriatric nursing programs. Geriatric nursing services are provided at chronic and intensive care settings or outside the hospital settings and the objective is to improve and preserve functional capabilities and help the elderly to use their energy to improve their independence. The nurse helps the patient to preserve maximum physical abilities and the ability to carry out continence affairs and adapt to spiritual, mental, social, and physical limitations. The competent and authorized geriatric nurse has specialized knowledge about acute and chronic changes in the older adults [13].

Conclusion

The findings indicated an inverse relationship between social isolation and the quality of sleep in older adults. To improve the quality of sleep in older adults, nurses and cares providers need to provide the ground for more social interactions. In addition, with higher quality of sleep, older adults can have better social interactions. Proper education about preparing the ground for social interactions in older adults should be provided to the nurses and geriatric cares providers. In addition, the environment and mood of older adults must be managed to improve their quality of sleep. Communication skills with older adults must be a part of the education provided to nurses and nursing programs. In addition, further studies in this field may shed more light on all aspects of the topic.

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The effect of the mind concentration / relaxation of body and soul (recovery) in karate sports students after a session of karate practice in Gorgan

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Abstract

The purpose of this study is to investigate the effect of mind concentration / relaxation of the body and soul (recovery) on sport students. This is semi-experimental research with pre-test and post-test design. The statistical population of this research included all men aged between 20-40 years old in the karate field in Gorgan. The sample included 21 athletes who were selected through availability and voluntary sampling method. The used instruments included General Health Questionnaire (GHQ). Data were analyzed using covariance analysis methods. The results of covariance analysis showed that the effect of mind concentration / relaxation of body and soul (recovery) on sport students was significant.

Key words: Concentration of mind, body and soul, athletes.

Introduction and statement of the problem

In the field of martial arts after long and intolerable exercises athletes reach the weakest performance at the end of the training which has caused them a great physical and mental challenge. Physical challenge is due to the production of lactic acid and pain in the muscles of the body and the psychological challenge due to thinking of absorbing pain in mental spaces. Mental exercise is as effective as physical exercises on players' achievement. These exercises can put normal athletes, as a result of aerobic exercises lactic acid production as well as high and slow heart rate returns to a normal and natural state (Fooladvand, 1393).

One of the inevitable aspects of sport competitions is competing in tense circumstances. Depending on the athlete's perception, these conditions are interpreted in different ways. In the case of understanding the competitive situation as a threatening condition and responding to this situation with tension and stress, competitive anxiety is created in an athlete.

Much research has been done on the effects of anxiety on athletes' performance (Wolf, Eys and Kleinert 2014).

One of techniques used to reduce the sport symptoms, which has been largely investigated in terms of its effectiveness and success is meditation or therapeutic treatment; all research indicated the beneficial effects of this technique (Bernard, 2012).

Meditation is considered as one of today's modern treatments that is used by psychotherapists and physicians based on thoughtful aspects of modern psychotherapy. Meditation is a relatively new therapeutic approach that is composed of ancient and new methods of meditation. This different cognitive methodology teaches people the ordinary attitudes. This new attitude can create new therapeutic horizons in the mind of the athlete. Meditation can meet the supervised care needed for a limited time (Amanz, 1392).

The effects of meditation are deep and rapid, therefore using it reduces the length of treatment sessions, so the patient can quickly gain their mental and psychic balance (Lee et al., 2011). The researcher has proposed an integrated approach to mind consciousness with cognitive-behavioral intervention. The most common method of teaching mind consciousness is mind training and awareness of anxiety reduction which is known as anxiety decrease and tranquility program (Omidvar, 2011).

Relaxation is used as an effective treatment for anxiety disorders. In Bastani et al's study in 2012 applied relaxation is a combination of muscle relaxation and respiratory techniques which have a main role in reducing athletes' stress levels.

The progressive muscle relaxation method was introduced by Edmond Jacobson in 1934. This method is a component of cognitive-behavioral therapy that is designed to reduce the stress and anxiety through muscle relaxation (Saeidi 2012: 10).

Progressive muscle relaxation is a non-invasive, low-cost, uncomplicated method that can be done independently by the individual. Muscle relaxation is a systematic treatment for controlling anxiety, insomnia, high blood pressure and digestive disorders such as indigestion and leads to deep relaxation (Shobeiri et al. 1394:3).

Hippocrates believes that relaxation can dramatically change the activity of auto nerve. As a result, it affects a person's physiological response to stress. Martin (2013) and Lau (2010) mentioned relaxation techniques as an integration of a variety of psychological-physical and cognitive-behavioral interventions to balance the psychic and emotional functions in mental and physical reactions (Lau, 2010).

The purpose of this study is to create awareness of muscles tension and relaxation. The meaning of relaxation progression is that muscle contraction movements begin at regular intervals with head, neck and face muscles, then include the middle and end organs of the body. In this method, the person by doing contraction movements and returning them deliberately to relaxing position increases blood flow and improves the blood supply of organs (Kordi et al, 2012:19).

One of the used approaches is relaxation intervention. Relaxation is a combination of cognitive-behavioral and psychic-physical interventions that balances mental and emotional functions and by making appropriate physical and mental responses reduces the physical and mental stresses (Lau and Macmain 2005).

Techniques of this therapy are classified in 2 groups:
First group techniques focus on physiological responses (Jacobson breathing training) that range from muscular exercises to mental exercises (progressive muscle relaxation). Second group includes various types of relaxation such as meditation which begins with mental exercises and finishes with muscle relaxation (relaxation based on mental imaging). In second group techniques, the athlete reduces non-adaptive behaviors, mediates negative thoughts and focuses on anxiety control before the competition (Watanabe, Fukuda, Hara, Meada,Ohira et al. 2006). Evidence suggest that progressive muscle relaxation can have important physiological and psychological benefits simultaneously with anxiety control (Morris, Pittle &Watt 2005). Additionally, other advantages of relaxation are its simplicity, practicality and usefulness. Many studies have examined the efficiency of relaxation techniques in the field of sport. In this regard Elion, Aziz, Rahim and Foad (2013) in a study on young soccer players concluded that relaxation is effective in reducing the anxiety of competitive position. Also, Solberg et al (2000) examined the effect of relaxation and showed that the use of relaxation methods reduce anxiety in runners and improves their performance. Fisher (2007) indicated as well that deep breathing in young tennis players is effective as a relaxation method for reducing competitive anxiety. Generally, in sport competitions the role of psychological factors is very significant. According to Field et al (2005), it can be said that muscle relaxation can reduce cortisol secretion by reducing body anxiety and sympathetic activity. Muscle relaxation through a systematic set of physiological changes reduces the oxygen consumption, heart rate, respiratory rate and blood lactate which are signs of decreasing symptoms of anxiety in the individual. So relaxation is a behavioral therapy that is simple, practical and useful which doesn't require special equipments (Alsone 2013) and can be applied after a brief training (Hamidi, 2015). There are diverse relaxation techniques that include progressive muscle relaxation, guided visualization, massage, hypnosis, yoga, music therapy and respiratory techniques (Hamidi 2015).

Progressive muscle relaxation involves exercises that shrinks and then relaxes the selective ultra-group muscles until it reaches a deeper relaxation state. This process increases the blood circulation and improves the function of bloodstream to body organs and stress relief of muscle reactions is related to anxiety reduction (Dorris, 2011).

In Traga study (2014), progressive muscle relaxation along with respiratory techniques has been reported effective to reduce the amount of anxiety in athletes.

As a result, progressive muscle relaxation will bring calmness to the nerves and muscles and subsequently the brain and heart will return to the state before exercising. Therefore, the present study seeks to answer the question of whether the concentration of mind on body and mental relaxation in karate students is effective after a karate practice session or not.

Significance of the study

The performance of motor skills has always been a matter of interest since basic skills are acquired from the very beginning. Movement is one of the most fundamental factors in human life and has an important role in general development, especially mental development (Rahimi Arsanjani, 2012).

Many studies have shown that sport in addition to being a valuable tool for maintaining physical health, has a close relationship with mental health and in particular prevention of mental and psychological abnormalities (Vaez Mousavi, 1393).

Exercise and physical activity not only contribute to fitness but also play an important role in preventing diseases, especially mental illness (Rahimi Arsanjani, 1391).

The necessity and importance of exercise in general affects overall body development. Exercise is not just a simple activity, it strengthens complex brain functions in various matters such as coordination, agility, correct behaving, decision making and so on, and affects all components of the body, soul and mind. With the activity of the brain while exercising in some hours of the day, all feelings, fatigue, boredom and weakness will be resolved to a great extent. Regular exercising can be tranquilizing if it is sustained. This relief will reduce anxiety, brings passion and exercise therapy (Fox, 2011).

This research attempts to identify and determine the scientific relation, logic and the effectiveness of mind variables on the relaxation of the body and psyche. It is hoped that the findings of the research could provide a platform for athletes, experts, managers and sport organizations to use these findings to enhance and improve the health of the organization. The purpose of this study is to investigate the effect of mind concentration on the relaxation of body and mind in athletes in Gorgan.

Research Methodology

In this method, a semi-experimental research with pre-test and post-test design was used. The statistical population consisted of 20 to 40 year old men in karate major. The statistical population of this study was 30 and of these, 21 people were willing to participate in the study; they were selected and tested by General Health Questionnaire (GHQ).

Research Instrument

General Health Questionnaire:
The 28-item form of the General Health Questionnaire has the advantage of being designed for all people in the community. This questionnaire as an instrument can determine the possibility of a mental disorder in a person (this questionnaire has 4 subscales, subscale of physical symptoms, anxiety and insomnia, social failure and depression). The duration of the test is 50 minutes on average.

The scoring methodology is that from option A to D, the score zero, one, two and three is given. The test is due to answering this fundamental question: what does the test measure and to what extent does it have practicality and validity?

Williams, Goldberg and Marie (1998) quoted by Yaqubi (1995): the results show that the mean sensitivity of 28-GHQ is 82% (between 78% to 85%). In Palahang research, the sensitivity, particularity and test practicality were 88%, 74% and 80% respectively; Yaqubi and Palahng used Likert method. In a study of 223 adults, Chong and Spears (1994) quoted from Jacoby concluded that the reliability coefficient retest of GHQ-28 is 0/55 and the reliability coefficient is gained through retest from 42 to 47 percent for its sub scales. In addition, the coefficient for the overall scale was 0/88 and for the sub-scale between 0/66 to 0/88.

Procedure

After implementing the general health questionnaire as a pretest, the subjects were randomly assigned to the experimental and control group. The subjects of the group are tested. They received the test of mindfulness on relaxation as a group (with homework assignments during meetings, at home and group discussion) 8 sessions (each session lasting 90 to 120 minutes) at the gym. After completing the sessions, each group was again tested by a general questionnaire.

The content of mind consciousness sessions based on body and soul relaxation

Three Theoretical sessions

First theoretical session (The duration of the class is one hour): The first session, the topic of meditation (focusing on the mind) of hypnosis (waves: beta, alpha, theta, delta) and energy systems (transcendental body), a brief explanation for absence of mind dynamics and to recognize the of the methods functions.

Second theoretical session (The duration of the class is one hour): the second session includes the topic of self-conscious mind and how to enter it, conditions of attending this mental space, mental training and the progressive relaxation theory training, which runs rapidly from the lower legs up to the head. But it is according to a specific standard which I define in class, teaching hypogastric breathing and visualization.

Third theoretical session (The duration of the class is one hour): the third session includes the topic of unconscious mind and how to enter it, conditions of attending this mental space, mental training and the progressive relaxation theory training, which runs rapidly from the lower legs up to the head. But it is according to a specific standard which I define in class, teaching hypogastric breathing and visualization.

Practical session

The first practical session (the duration of the class is one hour): At the first session, the topic of progressive relaxation muscles from the lower body to the top of the body is practically implemented. In addition, hypogastric breathing and visualization by means of mental regulation (the master organizes and regulates the mental structure).

The second practical session (the duration of the class is one hour): At the second session, the topic of progressive relaxation muscles from the lower body to the top of the body is practically implemented. In addition to hypogastric breathing, visualization and mental relaxation (the master cleans up the negative thoughts and images from mental structure.)

The third practical session (the duration of the class is one hour): The third session involves the subject of progressive muscle relaxation, along with hypogastric breathing, mind visualization, the creation of conscious mind space, the entering and exit, attending this mental space and identifying the negative and positive factors inside it.

The fourth practical session (the duration of the class is one hour): The fourth session involves the subject of progressive muscle relaxation, along with hypogastric breathing, mind visualization, the creation of conscious mind space, the entering and exit, attending this mental space and identifying the negative and positive factors inside it.

The fifth practical session: The fifth session involves the discussion of progressive muscle relaxation with hypogastric breathing and mind visualization, entering the space of conscious and subconscious mind, and then visualizing the transcendental body, finally calming all these spaces.

Research Analysis

In analyzing the data, considering the fact that in this distribution, the pre-test-post-test with control group was used and considering the normal distribution of the scores and homogeneity of variances, the covariance analysis was used and the data was analyzed using SPSS software.

In this section, the data regarding the demographic characteristics of respondents are analyzed by drawing the averages tables.

Table 1: Frequency distribution of athletes according to marital status

Marital status	Frequency	Percentage
Single	10	47.5
Married	11	52.5
Total	21	100

As the table shows, nearly half of athletes are single and the other half is married.

Diagram 1: Frequency distribution of athletes in terms of marital status

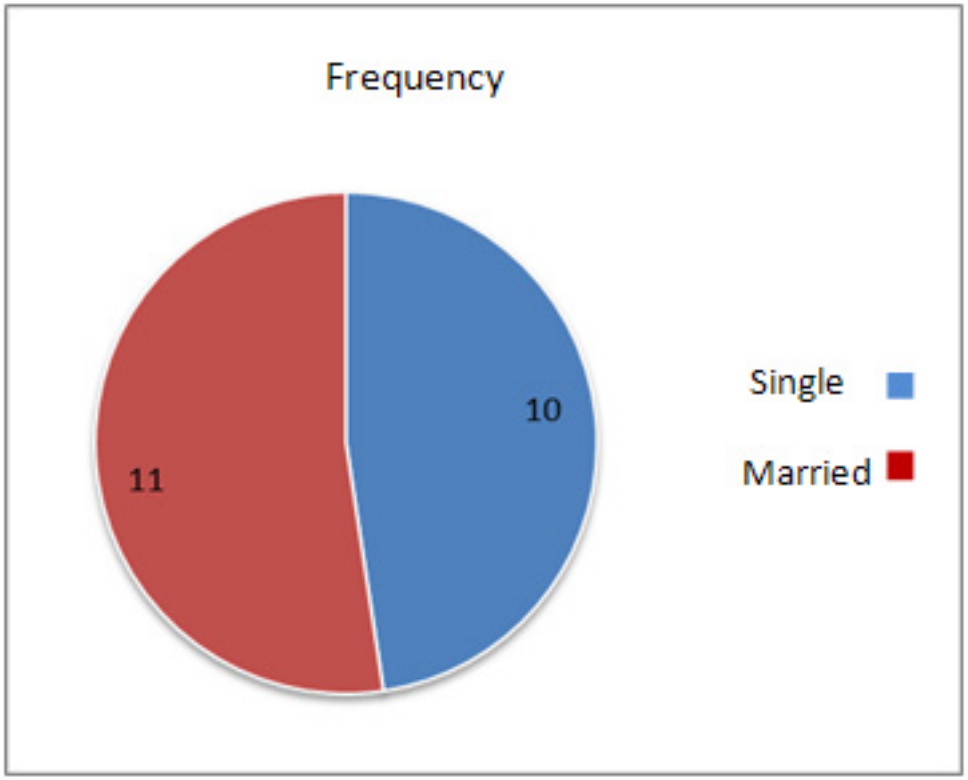


Table 2: Frequency distribution of athletes in terms of educational level

Education level	Frequency	Percentage
Secondary education	1	4.7
Diploma	2	9.5
Associate degree	5	23.8
Bachelor of Art	8	30
Master of Art	5	24
total	21	100

According to the table, 30% of sample size have bachelor degree and 24% have master degree. The other results are shown in diagram 2.

Diagram 2: Frequency distribution of athletes in terms of marital status

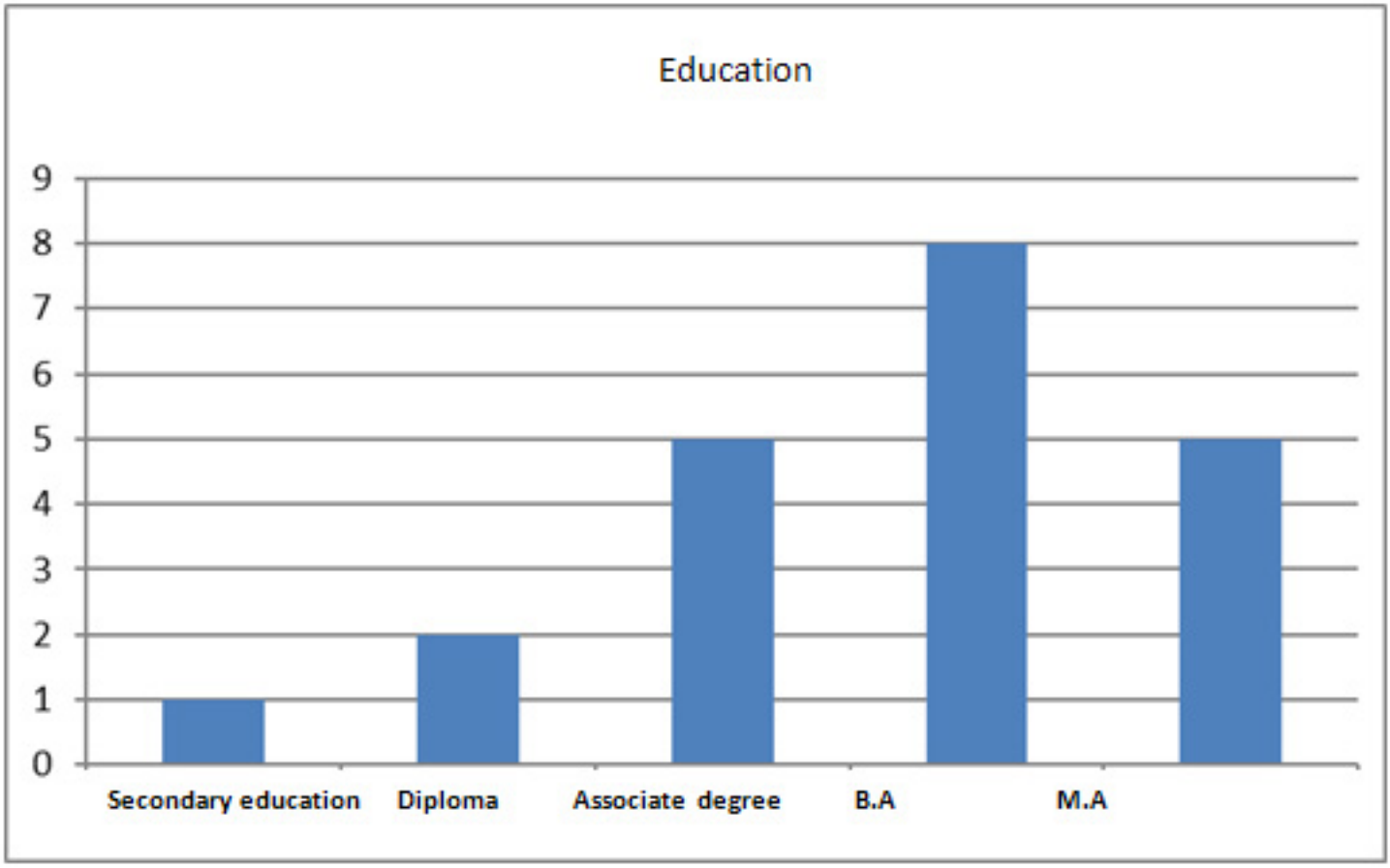
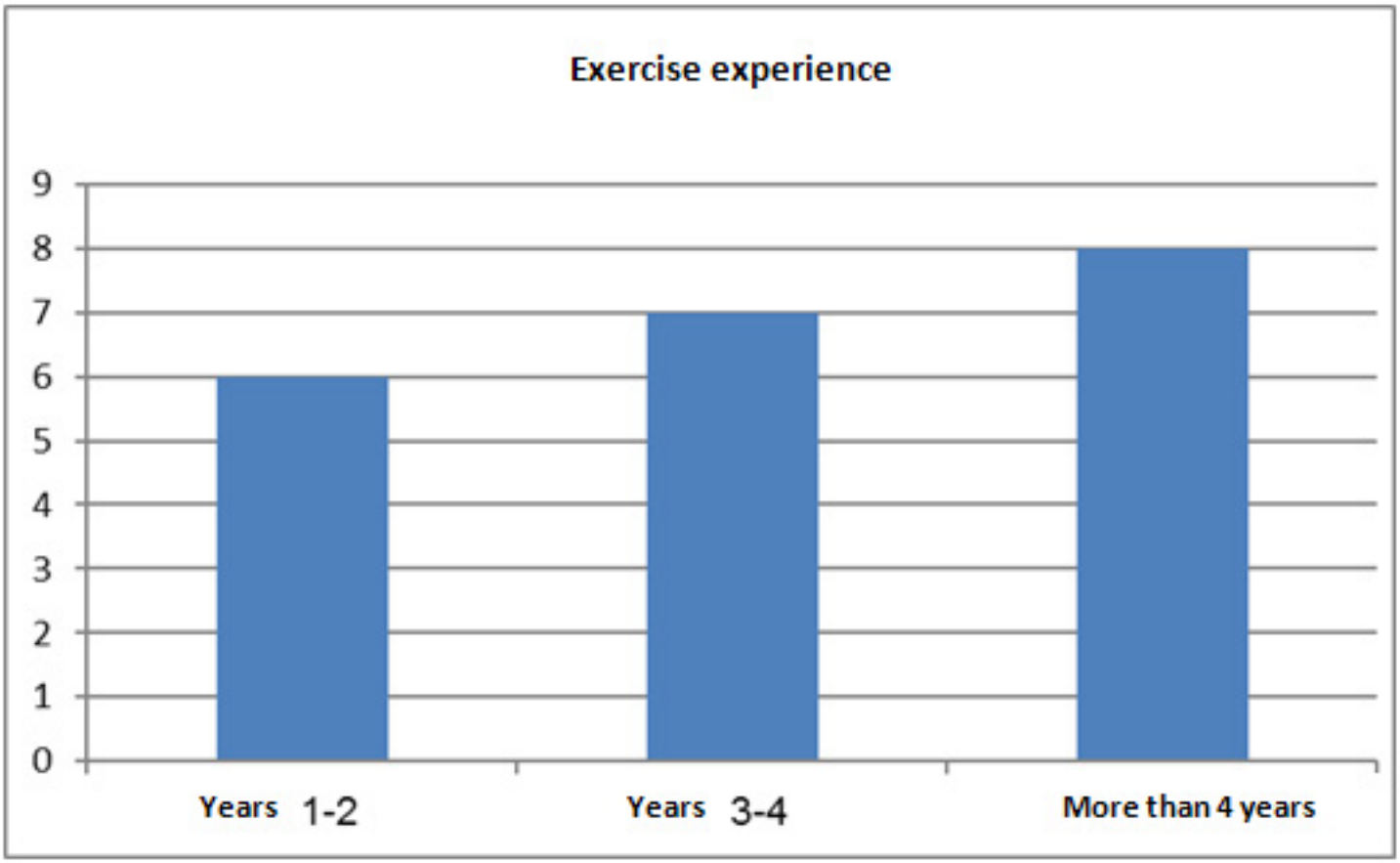


Table 3: Frequency distribution of athletes according to the exercise experience

Exercise Experience	Frequency	Percentage
1-2 Years	6	28.5
3-4 Years	7	33.5
More than 4 years	8	30
Total	21	100

The obtained data shows that 33% of athletes have 3-4 years of exercise experience. Other results are shown in diagram 3.

Diagram 3: Frequency distribution of athletes according to the exercise experience



Data Normality test

The assumption of the data normality at the significance level of 5% was tested with the Kolmogorov-Smirnov technique. The results are presented in Table 4. As shown in the table, a meaningful value greater than 0.05 is obtained. Therefore, there is no reason to reject the zero hypothesis based on data normalization. In other words, the data is normal.

Table 4: Results of the Kolmogorov-Smirnov test

Effect of mind concentration	
3.63	Mean
0.82	Standard deviation
1.21	Kolmogorov statistic
0.10	Significance level

At this stage, the inferential statistics of the data analysis are presented in the form of the following tables.

Table 5: The mean of pre-test and post-test in athletes

Standard deviation	Mean	Number	Test
0.26	3.2	21	Total DHS of pre-test
0.10	3.7	21	Total DHS of post-test

According to Table 5 the mean of pre-test and post-test in total indicates the athlete's tested factors.

Table 6: ANOVA test results for athletes

Significance level	Frequency	Mean of squares	Degrees of freedom	Sum of squares	Variable Index
		3.07	1	3.0711	Between group
0.000	77/05	0.03	40	1.5943	Within group
		-	41	4.653	Total

A look at the results presented in Table 6 shows that the observed F (77.05) resulting from the multivariate analysis of variance analysis on the two groups of pre-test and post-test scores in athletes was statistically significant. According to the critical value, it is significant ($p < 0.05$). It can be perceived that the assumption H0 is rejected and the H1 assumption is accepted. It can be concluded that at confidence level of 99%, there is a positive and significant relationship between mind consciousness and karate athletes. This means that mental visualization can have an effect on conscious and subconscious mind.

Discussion and Conclusion

The purpose of this study was to investigate the effect of mind concentration on body and soul relaxation in karate sports students, to analyze and explain the state of mind concentration, to gain scientific and realistic insight into the achievement of information in this field.

The results showed that the mind concentration group significantly relaxed body and soul in athletes. The findings of this research are based on the research carried out in Iran and abroad, Mardani and Shahraki (1393), Besharat and Sharghi (1394), Besharat (1395), Rahgozar and Taheri (1395), Casten and Winch (2011), Pathy and Safford (2013), Lavy (2015).

Sports experts believe that mental exercises are as effective as physical exercises in increasing the success of athletes in various sports. By examining the reasons behind the success of professional athletes like Bruce Lee, Andy Hooke, Masutatsu Oyama... It is clear that one of the ways of this success is their ability to visualize. Visualization and mental imagery can be influential in the various aspects of human life. Mental visualization can have an effect on conscious and subconscious mind.

It can be stated that physical activity or exercise stimulates the muscles and increases the activity of body organs. Also the brain and mind of man are not excluded. With brain activity during exercise, all imaginations, fatigue, impatience and weakness will be significantly reduced. Regular sports activities, if continued, can make the mind more relaxed, and this relief makes learning easier and more willing to work. Exercise, in addition to being a valuable tool for physical health, has a close relationship with mental health and, in particular, the prevention of psychological abnormalities. Exercise reduces anxiety and depression, increases self-confidence and enhances self-esteem. In the course of intense exercise, the level of endorphins secretion increases, which is why athletes feel pleasure and relax afterward. In this technique, the athlete feels in a challenging situation that may be stressful. In this case, he can predict possible happenings and practice for success, with the assumption that he can successfully overcome such difficult and challenging conditions. Positive thinking can change mood and cause mental readiness before a match. Therefore, one of the success keys in successful athletes is the use of mental exercises to achieve relaxation for the proper use of their mental capacities, which can be easily accomplished through comfort and repose arts and by gaining mastery, physical, emotional and mental relaxation can be achieved. Athletes, who learned mind concentration, were able to perform their athletic skills and karate arts better during training. Their sleep disorders have improved, according to karate students and athletes' declaration. The recovery and returning body to the original state were better done by using mental practices. Anxiety and stress resulting from exercise and athletic tournaments were dramatically reduced by mental exercises.

Suggestions

1. It is suggested that this research be carried out on all sport fields.

2. It is suggested that the effect of mental exercises prior to the onset of exercise on athletes' readiness will be studied during the exercise.

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Analysis of the effect of resveratrol and quercetin separately and together on Wnt Signaling path regulators, tumor differentiation, dietary intake and weight changes in rat's empirical colon cancer

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Abstract

Cancer is one of the most common diseases in the world. 1 out of 8 deaths in the world happen as a result of cancer. Cancer is the third cause of mortality in Iran. Colon cancer is the fourth cause of mortality at the world and annually 1.2 million people with the disease are being diagnosed. About 8% of overall mortality rate is associated with colon cancer. Colon cancer has considerably increased in Iran over the last 3 decades and it is the second most common cancer in Iran according to the annual report of National Cancer Institute of Iran. Spread of colon cancer in Iran can be estimated to be 8 out of 100,000 people. 3,641 new cases of cancer are reported annually in Iran and 2,262 people die in Iran every year as a result of colon cancer. Spread of the disease in the Iranian population is equal to 22% and accordingly and because of conflicting reports on effectiveness of resveratrol and quercetin in different steps of cancer, and lack of existence of study on simultaneous effect of the two compounds on colon cancer in vivo, this study intends to evaluate their effect together, so that positive results obtained from this study can be generalized to human studies.

Key words: resveratrol and quercetin, Wnt signaling path regulators, empirical colon cancer

Introduction

Colon cancer is the fourth cause of mortality in the world and the second most common cancer in the Europe (1). About 8% of the overall mortality rate caused by cancer is due to colon cancer. The highest increase rate is reported in Asia and Eastern Europe (2). According to the statistics of the World Health Organization (WHO), 1 million people with colon cancer are being annually diagnosed across the world (3). Colon cancer has significantly increased in Iran over the past 3 decades and is the second most common cancer in Iran according to the annual report of the National Cancer Institute of Iran (3). Spread of colon cancer in Iran is estimated at 8 out of 100,000 people (4). 3,641 new cases of cancer are reported annually in Iran and 2,262 people die in Iran every year as a result of colon cancer (5). Spread of the disease in the Iranian population is equal to 22% (3). According to the relevant studies in Iran on colon cancer age distribution, this cancer is happening in a younger population compared to western countries (6).

Early diagnosis of colon cancer over the years has played a key role in survival, since chemotherapy drugs can prevent excessive proliferation of cells in special body organs and apoptosis induction in tumor cells (7). However, one of the most important problems is that the recent medical methods for advanced colon cancer steps have imposed damaging effects on the health system and on the patients (8).

Common Cancer treatments

While this paper concentrates on chemotherapy, Radiotherapy and Surgery are other common medical treatments and choice of method of approach depeneds on the type of the cancer and the location of the cancer.

Chemotherapy

The common chemotherapy approach is as follows: the effective chemotherapy agent is taken orally or infused into the body by IV route and the agent affects some other cells and tissues in addition to cancerous cells and more importantly, it can damage the adjacent tissues and the entire bodily system (7). Effectiveness of treatment is not satisfying even with development of new anti-cancer drugs and the American Society of Clinical Oncology (ASCO) emphasizes necessity of finding a new approach to treat cancer. The main objective of colon cancer treatment is purposeful use of cancer chemoprevention materials (9).
Sliddique et al (10) analyzed the effectiveness in cancer through prescription of one or more natural or synthetic substances preventing cancer relapse or slowing down cancer progress as a chemoprevention mechanism.
The main objective of chemoprevention is identification of natural components of edible plants, or molecules which can prevent cancer cell growth or metastasis through interference with intercellular paths of cancer cells (9).
The main mechanism for chemoprevention can be natural components of certain plants including modulation in expression of genes regulating cell proliferation, modulation in differentiation, modulation in apoptosis, and stopping angiogenesis and metastasis (1).

The most effective compounds of cancer treatment monitoring

The components and contents of natural components of different ingestable materials are the most reliable compounds to monitor cancer treatment, since their effects have been studied in the field of accidents related to cell process and Pleiotropic nature of target tissue and non-toxicity for normal cells, over the years. Food materials can be considered as environmental factors responsible for 20-30% of cases of colon cancer, since food materials can determine the microenvironment of colon cancer cells and the interaction of cancer cells and the microenvironment around the cell can also affect tumor growth (2).

Among chemoprevention factors reducing cancer risk, phytochemicals can be the most effective factor (12-15). The majority of studies conducted over the past 3 decades have introduced the extracts of plants as suppressing factors or as a factor causing delay of spread in types of cancer. These results are consistent with the results of epidemiologic studies showing that using fresh green and yellow fruits and vegetables can decrease cancer and mortality in colon, breast, prostate, esophagus and bladder cancers (14, 16, 17). Phytochemicals are herbal non-nutritious compounds with disease prevention properties with anti-cancer effects (18).

According to the book “Fundamentals of Cancer Prevention”, prevention of cancer can be classified in 3 steps: Step 1 (mainly avoiding carcinogens); Step 2 (detection and removal of benign lesions) and Step 3 (prevention of cancer relapse and tumor progress).

Phytochemicals in 3 steps can have preventive effects on cancer from the beginning of tumor creation to all factors affecting cancer (cell proliferation, apoptosis, inflammation, genome stability) (11, 18).

As 2 main hallmarks of cancer cells include misplaced cell proliferation and resistance to apoptosis, identification of natural components of edible plants can be the most reliable compound (because of non-toxicity) to monitor cancer treatment (19, 20).

The effect of resveratrol on cancer treatment

One of these compounds is resveratrol, a natural substance (3, 4 and -5 3-hydroxy trans Acetylbenzoic acid) with abundant biologic effects on prevention and treatment of cancer. Resveratrol is a phytoalexin compound or antibiotic of the plant, which is produced in the plant in large amounts in response to environmental stress and pathologic invasion and acts therefore as natural inhibitor of cell proliferation (21, 22). The compound can be produced from Cinnamon radical transplantation (23). Resveratrol has been found in more than 70 plant species including grapes, berries, plums, peanut and pines (21). Over the

decade, it has been demonstrated that resveratrol has a wide range of pharmacologic properties. It seems that additional biochemical and molecular activities of the compound can cause the effects of resveratrol in cancer and pre-cancer cells (11, 22).

The information has resulted in conducting a large number of basic animal studies to analyze potential effects of resveratrol as a cancer chemoprevention substance. Moreover, resveratrol imitates calorie restriction and improves health and interferes in the ageing process (22). It has been reported that resveratrol can inhibit accumulation of platelets and oxidation of LDL, nitric oxide synthesis and vessel expansion in vivo (19) and inhibition of smooth muscle cell proliferation through reducing Cyclin A gene expression (24). Moreover, the compound can cause suppression of cancer cells (in vitro) (1) and reduction of tumor growth in animal models (13). The anti-cell proliferation mechanism of resveratrol is well identified. Recent studies have shown that resveratrol can cause apoptosis induction in cancer cells through increasing P53 gene expression (25) and decrease in Bcl-2 gene expression (26).

Red grape contains a substance called resveratrol, which can make a kind of conventional protein called serotonin in the human body and the protein can also maintain the youth of human chromosomes. According to studies, red grape contains substances reducing the risk of cancer and physical inflammation (10). Grape prevents cancer cell proliferation. Dr. HA Taj Mirriahi, researcher in Chemistry-Biology Department of Quebec University of Canada, analyzed the molecules in red grape called resveratrol and showed that a combination of the substance can prevent excessive proliferation of cancer cells in the body. Accordingly, resveratrol is a natural substance separated from grape shell and seed and because of special interaction of the substance with DNA and with its inhibitory effects on some malignancies; it can play a key role in cancer prevention and decreased cancer lesion growth.

The effect of quercetin on cancer treatment

The structure and biogenesis: polyphenols are secondary plant metabolites and protect plants against ultraviolet radiation, oxidants and pathogens. Flavonoids are the most frequent polyphenols of human dietary intake. Flavonoids include Anthocyanins, flavonols, flavanols, flavvounes, flavones and isoflavones and 4- Pentahydroxy Flavone; Quercetin with its structure (3, 5, 7 and 43-9) is one of the most important examples in the group of flavonoids (11).

Food sources: quercetin-rich food sources include fruits and vegetables, especially red onion, apple, berry and citrus, tea, nuts and seeds. In these materials, quercetin is mostly observable in the form of glycoside quercetin with low intake ability and in the case of hydrolysis 68% glycoside (1, 9, 10, 12, 13) the intake of the substance reaches to 81. Average daily intake of quercetin in humans is not specified although complete intake of polyphenols is 1 gr per day and two thirds are in the form of flavonoids (14).

The effects and pharmacology: the main known effects of quercetin can be its antioxidant effect, prevention of accumulation, muscle relaxation, platelet LDL, prevention of smooth vein oxidation, reduction of serum fat levels, reduced systolic hypertension, weight loss in animals and reduced plasma insulin, reduced level of plasma inflammation markers and anti-cancer effects (1, 9, 12 and 14). It has been found that antioxidant effects of quercetin are at a high level under conditions of high inflammation and high oxidative stress (9). The place of quercetin accumulation can be in liver and it can be disposed of mainly by urine and through bile (9, 10). According to the studies, quercetin can inhibit cytochrome enzymes.

The mechanism proposed for anti-cancer effects of resveratrol include cell death induction through regulating Fas level in cell membrane producing extracellular apoptosis (27-29), prevention of caspase activity (30, 31), reduced inflammation through suppression of products of gen es regulated by NFKB (31), reduced production of relevant proteins of cell cycle (expression of kinases associated with cyclin E, Cdk4 and D1 cyclin) (32, 33), increased expression of SIRT1 (a gene relevant to reduced Survivin expression), cell lifetime and slowing down he ageing process (34) and inhibition of Wnt path (35).

Quercetin is the second flavonoid in plant species, which is available in fruits and the majority of vegetables (36) and can be considered as an anti-cancer compound. Cancer prevention effects of the compound can be attributed to antioxidant activity of quercetin and inhibition of enzymes activating carcinogens, regulation of intracellular signal transfer path and interaction of quercetin with receptors and other types of proteins (37).

Among the molecular anti-cancer mechanisms proposed for quercetin, one can refer to direct effect of quercetin on reduced activity of Cyp1A7 in colon cancer (plays a role in activation of carcinogens) (37), effect on estrogen-dependent receptors and inhibitory effects on expression and function of androgenic receptors (similar activity of phytoestrogens) (38), apoptosis induction through Mitochondrial path (caspase activation) (3, 9); reduced Bcl-xs/Bcl-2 ratio and increased Bax (39), affecting DNA failure, failure of Poly (ADP-ribose) Polymerase (PARP) and increased Bax and affecting Bcl-2 level (anti-apoptosis) (39), reduction of synthesis of inflammatory cytokines and iNOS (Inducible nitric oxide synthase) expression (40).

Quercetin and resveratrol are both the polyphenols in red grape. It has been demonstrated that simultaneous intake of quercetin and resveratrol can reduce restenosis level (probably through inhibition of smooth vein cell proliferation). Therefore, using a combination of quercetin and resveratrol has high potential to control cancer (41).

Moreover, quercetin can inhibit sulfate of resveratrol and hence, it may increase biofeedback and as a result, medical quality of resveratrol through a sulfate process. However, further studies are needed in this field (22).

Discussion

It seems that among all mentioned mechanisms, apoptosis induction and cell proliferation inhibition are the most common underlying mechanisms affecting anti-cancer activity of phytochemicals, since effective drugs for cancer treatment can cause apoptosis induction (42). Stop of cell cycle is a hopeful strategy in cancer prevention. Cell cycle includes 4 steps respectively including G1, S, G2 and M (43). Abundant factors and proteins in positive or negative functions on various controlling points regulate control the cycle carefully. In the case of existence of ideal factors (quercetin and resveratrol), cancer cells fall in apoptosis in step G1; otherwise, phase S is begun with increased time of treatment of the cancer cell. With the continuity of presence of ideal factors (quercetin and resveratrol), with increased treatment time of the cancer cell, apoptosis is induced. Cell proliferation plays a key role in multiple steps of cancer creation with multiple genetic variations. Therefore, cell proliferation control is important for cancer prevention (44). Quercetin and other flavonoids can inhibit colon cancer cell proliferation (1) and stomach cancer cells (45). This can be achieved mainly through blocking cell passage from step G1 to step S.

The best path in cell proliferation in colon cancerous cells is the Wnt path. Exploration of the first Wnt gene was done in vertebrates (Wnt1 gene in rats). The term “Wnt” is a combination of Wing Less and Int for integration of Retrovirus in rats. Wnt path activation can control important evolutional events such as brain evolution, hand and feet pattern and organogenesis. Moreover, Wnt messaging is underlying in controlling stem cells and in many other aspects of evolution. Dysfunction in messaging through Wnt is associated with various cancers such as colon cancer. Wnt can be activated through two protein receptors of cell level (Frizzledz), which is directly connected to Wnt and an aid receptor, which seems that it is connected to Frizzledz in the path of Wnt messaging. According to the proposed model of Wnt path, the original and the central factor in Wnt intracellular message transfer is Beta-catenin in vertebrates and is Armadillo Vinegar in flies. The multipurpose protein acts in both functions of transcription activator and a connector protein of cell skeleton to membrane (45). In absence of Wnt message, beta-catenin is phosphorylated by a complex containing glycogen kinase 3, APC protein (tumor inhibitor) and oxyn (a cell skeleton protein). Then, phosphorylated beta-catenin is Ubiquitinized and is decomposed in proteasome. In presence of Wnt, oxyn is connected to Cytosolic duct recipient. The connection complex contains GSK3 and can decompose beta-catenin and prevents phosphorylation of beta-catenin by GSK3 and stabilization of beta-catenin in cytoplasm. Stabilization of beta-catenin induced by Wnt is also required for Dishevelled protein. The protein is connected to fz Cytosolic duct. Beta-catenin has been released and has been moved inside the core and acts there along with transcription factor (T cell factor) Tcf to control expression of target genes. The importance of stability and placement of beta-catenin is for this purpose that Wnt messages can affect beta-catenin in cell (cell skeleton, cytosol and core) (45, 46 and 47). Quercetin (44) and resveratrol (46) can reduce expression of cyclin d1 and D2, which play a direct role in progress of cell cycle. Moreover, it has been demonstrated that resveratrol has anti-cell proliferation effects and can cause pause in cell cycle in vitro (20).

Intervention with qurecetin in animals can reduce oxidant indicator (Thiobarbituric acid reactive substances) significantly. Moreover, the supplement amount with NASH is in a nuclear group (4) and is lower than the transcription factor group interfered in factor-like defensive factors against stress-related damage. When it is activated, it can activate antioxidant activity and can increase production of proteins to reduce cell stress. Expression of this factor can be significantly increased with quercetin supplement.

Results of reviews

In the study conducted by Schneider et al (2001) (47), the effect of using 0.01% resveratrol for 7 weeks through gavage on APCmin/+ was studied and it was found that production of Small intestine and colon tumors was reduced in the group getting resveratrol. Moreover, it was demonstrated that D1 cyclin and D2 cyclin was reduced in the intervention group, which could specify the effect of resveratrol on reducing expression of genes playing a direct role in cell proliferation and cell cycle.

In the study conducted by Wan et al (2002) (51), the effect of green and white tea and Epigallocatechin on beta-catenin was analyzed in HEK293 cells and it was found that Epigallocatechin can decrease beta-catenin level.

In the study conducted by Volate et al (2005) (48) under the title of “Modulation of aberrant crypt foci and apoptosis by dietary herbal supplements (quercetin, curcumin, silymarin, ginseng and rutin)” on F344 rats with colorectal cancer induced by Methane Azoxide, it was found that using quercetin to 1.5% in diet of rats could cause significant decrease in abnormal crypts in colon of rats (4 times reduction); although such effect was not reported for rutin independently. Moreover, it was demonstrated that using a supplement containing all mentioned compounds can reduce ACF (aberrant crypt foci) respectively to 2, 1.8, 1.5 and 1.2 times. Moreover, it was found that quercetin is stronger than other compounds to decrease ACF level and has increased apoptosis in rats more than other compounds (3 times increase). Analysis of caspase 9, Bax and Bcl-2 using Western blot method showed that quercetin can lead to apoptosis induction through Mitochondria. The effect was also reported for curcumin.

This study has proposed analysis of role of quercetin and other herbal compounds in reduction of pre-cancer lesions and apoptosis induction in colon.

In the study conducted by Sengottuvelan et al (2006) (46) on wistar rats, under intervention by Dimethylhydrazine to get colon cancer, it was found that resveratrol intake for 30 weeks in 3 time periods of 2 weeks before carcinogen

injection, 2 days after carcinogen injection and at the same time with carcinogen injection could reduce level and number of ACF in colon of rats. Moreover, it was found that the cell proliferation level could reduce Cycloxygenase 2 (COX-2) and Orentinine in carboxylase (increased at time of tumor growth) in serum of rats.

Moreover, it was demonstrated that size of ACFs was also decreased in crypts (especially in distal colon) and intake of resveratrol during the study time or before DMH (dimethylhydralazine) injection could have more effects on number of ACF and size of ACF.

In the study conducted by Dihal et al (2006) (49) under the title of "Quercetin, but not its glycosidated conjugate rutin, inhibits azoxymethane-induced colorectal carcinogenesis in F344 rats", it was found that intake of quercetin to 0.1, 1 and 10gr/kg in diet of rats for 38 weeks could reduce tumor creation and tumor size; although rutin showed no similar effect. Number of abnormal crypts in colon as a result of quercetin intake showed no significant difference. Quercetin intake was not correlated to food intake and weight of rats and their mortality.

In the study conducted by Majumdar et al (2009) (50) on HCT-116 cancerous cells of human colon, the effect of synergism of curcumin and resveratrol was studied. Cancer cells were injected from culture medium to ICR SCID female rats to make tumor. Then, curcumin was injected into rats at 500mg/kg of body weight and resveratrol was injected at 150mg/kg of rats' body weight for 3 weeks. Rats were divided into 4 groups in terms of curcumin and resveratrol intake. The first group received only resveratrol; the second group only curcumin and the third group both compounds at the same time and a group was selected as control group.

In this study, it was observed that the effect of resveratrol and curcumin together can lead to more inhibitory effect on cancer cells in vitro and even more combined than using them separately.

Also, it was found in this study that the effect of synergism of curcumin and resveratrol in less than 20mm is very strong. Moreover, it was found that resveratrol, similar to curcumin, can inhibit EGFR and IGF-IR in colon cancer cells and using them alongside can lead to a higher rate of inhibition in said factors. Moreover, cell proliferation in tumor after simultaneous intake of curcumin (40%) and resveratrol (38%) can be stronger than their effect independently (more than 50%). Moreover, the level of apoptosis in case of simultaneous use of the two compounds was increased at 70% compared to control group and number of apoptosis cells was also increased at 21.5% compared to control group. Moreover, the adherence to DNA of factor NFk-B was decreased at 67% (resveratrol and curcumin independently caused reduction of 30-35%).

In the study conducted by Martinez et al (2010) (51), the effect of resveratrol on colon cancer was studied. 30 normal people were maintained on low-resveratrol dietary for 2 weeks. Sigmoidoscopy was done for colon tissue and the participants again got high resveratrol dietary for 2 weeks and biopsy was done. It was observed that high resveratrol can cause weight loss and reduction of fat intake. Resveratrol can decrease cell proliferation through decreased Cyclin D1. Expression of several genes in Wnt path was decreased. Moreover, people above 50 years old showed higher level of oxyn, cyclin and cmyc and this could reduce the resveratrol level to the level of young people.

In 2012, a study was conducted by Khandelwal et al (41) on analysis of the effects of quercetin and resveratrol on hyperplasia inhibition in rats with carotid dysfunction for 2 weeks. The dosage of resveratrol intake was equal to 25mg/kg of body weight and quercetin was fed to rats to 10mg/kg of body weight. Compared to control group, resveratrol could cause significant decrease in Rastnosis, which was evaluated through intima/media ratio at 76%. The effect was not observed for quercetin independently. In simultaneous use of the two compounds, intima/media ratio was significantly reduced at 94%. Both resveratrol and quercetin and a combination of them could significantly affect platelet activity and endothelial function. However, simultaneous use of the two compounds had less effect on this activity. Simultaneous use of quercetin and resveratrol could have stronger effect of inflammatory markers compared to separate use of these compounds. In general, the results obtained from the study showed that using quercetin and resveratrol together can decrease rastnosis probably through the effect of their synergism on proliferation of smooth muscle cells and inflammation.

In the study conducted by Alizadeh et al (2012) (9) under the title of "Chemoprevention of azoxymethane-initiated colon cancer in rat by using a novel polymeric nanocarrier–curcumin", 40 rats were grouped in 3 groups including control, curcumin and curcumin- Dendrozumy groups. After 22 weeks of intervention, abnormal crypts were observed in the control group. The expression of beta-catenin in the control group with curcumin- Dendrozumy was significantly decreased compared to control and curcumin groups and this showed effectiveness of the compound in prevention of colon cancer in an animal model.

In the study conducted by Cai et al (2015) (7) on APCmin rats, a type of heritance colorectal cancer created by mutation in APC 850 gene was studied and the results showed that after intake of 7mg/kg body weight of resveratrol and 14mg/kg of body weight for 14 weeks, as a result of higher dosage of resveratrol, the number of adenomas was decreased at 22%. Despite this, in the same study, in the group using high fat diet, lower dosage of resveratrol could cause decrease in number of adenomas about 40% and the disease risk was also decreased at 52%. However, higher dosage of resveratrol was also effective in decreased number of adenomas (about 25% in high fat diet). Inhibition of tumor progress as a result of using resveratrol in both dosages was associated with adenoma cell proliferation (6.5 to 9.3%); although no change was observed in the control group using HFD.

High dosage of resveratrol was correlated to weight gain in both groups (males and females) and it seems that resveratrol has protective capability against effects of tumor progress in high fat diet without body weight loss. Moreover, it was demonstrated that using a supplement containing all mentioned compounds could reduce ACF respectively to 2, 1.8, 1.5 and 1.2 times. In addition, it was found that quercetin could decrease SCF more significantly than other compounds and quercetin caused more increase in apoptosis level in rats (3 times increase) than other compounds. Caspase 9, bax and Bcl-2 analysis using western blot method showed that quercetin can cause apoptosis induction through mitochondria. The effect was also reported for curcumin. This study has proposed studying the role of quercetin and other herbal compounds in reduction of pre-cancer lesions and apoptosis induction in the colon.

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The Effect of quercetin on induction of apoptosis and cell proliferation in experimental rat colon carcinoma

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Abstract

Colon cancer is the fourth cause of mortality in the world and the second most common cancer in Europe (1). About 8% of overall mortality rate caused by cancer is caused by colon carcinoma and the highest spread of colon cancer is reported in Asia and Eastern Europe (2). Among cancer preventive factors by chemical mechanisms reducing risk of cancer, Phytochemicals can be the most effective factors. Among the Phytochemicals, one can refer to quercetin. Quercetin is the second flavonoid in plant species, which is available in fruits and the majority of vegetables (36) and can be considered as an important cancer prevention compound. The cancer preventive effects of the compound can be attributed to antioxidant activity of quercetin, inhibition of carcinogen activating enzymes, regulation of intercellular signal transfer paths and interaction of quercetin with receptors and other proteins (37). According to studies, quercetin can inhibit sulfate and hence, it can increase biofeedback and treatment competency through inhibition of sulfate.

Key words: quercetin, apoptosis induction, cell proliferation, rat colon

Introduction

Any kind of abnormal cell growth causing natural change or mutation in a cell is called cancer. Cancer cells are not limited to common limitations in cell proliferation applied by the host. However, proliferation does not necessarily refer to cancer. Abnormal cell growth can be divided into two groups of neoplastic and non-neoplastic classes.

Non-neoplastic growth patterns
4 patterns of non-neoplastic growth are as follows:
1) Hypertrophy: it means increased cell size, which happenes mainly as a result of increased work load or hormone stimulation.

2) Hyperplasia: refers to reversible increase in the number of cells in a special type of tissue causing increased tissue mass.

Hyperplasia is considered usually as a natural physiologic response in the case of fast growth (like pregnancy and maturity)

3) Metaplasia: a type of mature cell is replaced by another cell type, in which no tissue is usually observed (e.g. replacement of tuber cell instead of squamous cell). In case of removal of factor, the process can be reversible; although it may be changed into displasia if the stimulation is continued. Metaplasia may be created because of inflammation, vitamin deficiency, irritation and various chemicals. One of the most common areas of metaplasia is in the cervix.

4) Displasia: in this mode, normal immature cells change in terms of size, formation or organization or a mature cell is replaced with an immature cell. Displasia stimulants have usually external sources (like radiation, toxic chemicals and chronic irritation). Displasia may return in cases of elimination of irritant.

Colon Cancer

Colon cancer appears in the form of some glands in inner wall of colon. Colon cancer has considerably increased in Iran over the past 3 decades. According to the annual report of the National Cancer Institute of Iran, colon cancer is currently the second most common cancer in Iran. Early diagnosis of colon cancer over the years has played a considerable role in survival, since chemical medicines can prevent seamless cell proliferation in certain tissues of body organs and induction of apoptosis in tumor cells. However, one of the most common problems in this field is that the recent treatment methods for advanced colon cancer can impose damaging effects on the health system and the patient. Effectiveness of treatment, even with development of new anti-cancer drugs, is not satisfactory and the American Society of Clinical Oncology (ASCO) has emphasized necessity for a new approach for treatment of cancer. The main objective of colon cancer treatment should be purposeful use of cancer prevention materials with chemical mechanism. Among cancer preventing factors with chemical mechanism causing reduction of risk of cancer, phytochemicals are the most effective materials. Phytochemicals are non-nutritious herbal compounds with disease prevention properties with anti-cancer effects. One of these compounds is natural material (3, 4, and 5-trihydroxytrans-acetilin) with abundant biologic effects to prevent and treat cancer. Another phytochemical is quercetin. Quercetin is the second flavonoid in plant species available in fruits and the majority of vegetables. Phytochemicals can have preventive effects against cancer from the beginning of creation of tumor to all factors affecting cancer (cell proliferation, apoptosis, inflammation, genome stability). The main mechanism is expressing preventive function of cancer with chemical mechanism of natural elements of edible plants including adjustment in expression of cell proliferation regulating genes, adjustment in differentiation, adjustment in apoptosis and prevention of angiogenesis and metastasis. Moreover, quercetin can inhibit sulfate and hence, it can enhance biofeedback and as a result, treatment competency through inhibition of sulfate. It seems that among all mentioned mechanisms, apoptosis induction and cell proliferation inhibition can be the most important mechanisms affecting anti-cancer activity of phytochemicals, since can cause induction of mechanisms in line with apoptosis similar to drugs for cancer treatment.

Therefore, treatment of advanced colon cancer steps can be considered as a challenge. Hence, analysis of the effect of quercetin in induction of apoptosis, cell proliferation level and colon cell abnormalities can be important. Because of conflicting reports on the effectiveness of quercetin in different steps of cancer and lack of studies investigating the two compounds simultaneously in colon cancer in vivo; the present study tends to evaluate their combined effect , so that the results obtained from the study can be generalized to human studies.

Quercetin

Quercetin is a polyphenyl product in plants. Quercetin is one of the most important and available compounds of flavonoid strain, since it has the highest antioxidant properties among other flavonoids and is even 6 times stronger than vitamin C. Quercetin is available in vegetables, fruits, onion, apple, red grape, citrus fruits, Brussel sprouts and tomatoes, Green tea and dark chocolate (11-13). The relevant studies show protective effects of quercetin against DNA factors, liver, heart, kidneys and neurons (14). Moreover, the compound has pathogenic effects (16) and also has anti-cancer, antiviral, antimicrobial, anti-allergic, anti-hypertension and protective property against cataract (17). Quercetin also has antioxidant and anti-inflammation properties and can cause serum level protection (13), Glutathione and reduced serum level of malondialdehyde and decrease of nitric oxide metabolism and formation of superoxide, as well as decrease of release of oxidizing and inflammatory mediators (19). The compound has protective effect against oxidative damage and with decrease in oxidative damage in alanine transferase of liver, prevents increase in alkaline phosphatase (ALP) and Aspartate transferase (GPT) (20). There is no comprehensive information in regard to the effect of quercetin on liver and kidney damage caused by Methotrexate and previous studies have investigated limited parameters (21). Therefore, the study also investigates the effect of quercetin on removal of the toxic effects of Methotrexate on liver and kidney tissue and antioxidant enzymes of liver and kidney.

Necrosis and Apoptosis

There are two general paths for death of a cell: necrosis and apoptosis.

In the definition of necrosis, it should be mentioned that the cell is damaged as a result of external factors like toxins, pollution, infection and cessation of blood supply. The damaged tissue is usually inflamed and creates abundant problems.

However, apoptosis is an intercellular process: apoptosis or programmed cell death is a kind of cell suicide. The main advantage of apoptosis compared to necrosis is that apoptosis is a predictable and controllable process in most cases and can be removed easily by macrophages .

Apoptosis

In the Greek language, apoptosis means fall of leaves of trees or petal fall in plants. The process taken in multicellular animals is a vital process in body cells. In an adult person, daily about 50-70 billion cells fall in apoptosis and 20-30 million cells fall in apoptosis in a 8-14 year old child.

When 1 cell has to suicide by apoptosis inductor, proteins called caspase come into action. Caspase proteins can affect the process of DNase production in cell and the DNase enzymes cause cell wrinkle through intercellular DNA destruction (cell contraction). In the next step, signals are given to Phagocyte proteins and hence, the apoptosis process is completed with Epofototic cell phagocytosis.
Apoptosis is a vital process during the evolution of multicellular animals. For example, destruction of the curtains between fingers and toes are taken in fetal steps during apoptosis. Moreover, during the evolution of the brain, more cells are produced than required. Therefore, those without production of synapse joints are destroyed during apoptosis. Apoptosis is also essential during the menstrual process.

The studies on apoptosis were developed in the years after 1990; that is, the time that its role in different diseases was specified. It is very important that apoptosis is not always a perfect procedure. Sometimes, cells enter into the apoptosis path wrongly and the wrong procedure can be because of presence of apoptosis irritants. For example, when a cell is exposed to free radicals or directed radiations or is affected by stress, apoptosis may happen. Sometimes, it happens reversely: cells under apoptosis don't enter the apoptosis path (like cancer).

Scientists try to control apoptosis procedure of cells and control the type of apoptosis cell to treat diseases such as cancer and AIDS, Parkinson and Alzheimer. Today, treatment of cancer is being undertaken using chemotherapy or radiotherapy based on target cell apoptosis stimulation.

Discussion and literature review

According to statistics of the World Health Organization (WHO), colon cancer is being diagnosed annually in 1 million people of the world (3). Colon cancer has considerably increased over the past 3 decades in Iran and according to the annual report of National Cancer Registry of Iran; it is the second most common cancer in Iran in terms of spread (4). Colorectal cancer spread in Iran is equal to 8 out of 100,000 people (5). It has been estimated that every year in Iran, 3,641 new cases of cancer happen and 2,262 people die annually as a result of colon cancer (6). Spread of this cancer in Iranian population is equal to 22% (4). According to relevant studies in Iran in the field of age distribution of colorectal cancer, this cancer is happening in a younger population in Iran compared to western countries (3).

Initial diagnosis of colon cancer over the years has played key role in survival, since chemotherapy drugs can prevent excessive cell proliferation in certain tissues of body organs and apoptosis induction in tumor cells (7). However, one of the most important problems is that the recent treatment methods for advanced colon steps can impose damaging effects on the health system and on the patients (8).

The common method of cancer chemotherapy is that the effective substance is entered into the body and the substance affects all cells and tissues in addition to cancerous cells and more importantly, it can damage adjacent body tissues (7).

Effectiveness of treatment is not satisfying even using new anti-cancer drugs and the American Society of Clinical Oncology (ASCO) emphasizes the necessity of finding a new approach for cancer treatment. The main objective in treatment of colon cancer should be purposeful use of cancer chemoprevention substances with a chemical mechanism (9).

Sliddique et al (10) studied the effectiveness in cancer through prescription of one or more natural or synthetic agents to prevent cancer relapse or slow down the disease progress as cancer chemoprevention.

The main purpose of cancer chemoprevention is to identify the natural components of ingestible plants preventing growth or metastasis of cells through interference of intercellular paths of cancer cells (9).

The main mechanism presenting the cancer chemoprevention is the natural components of ingestible plants including modulation in cell proliferation regulating gene expression, modulation in differentiation, modulation in apoptosis and angiogenesis and cessation of metastasis (11).

The contents and components of natural elements of different foods can be the most reliable compounds to monitor cancer, since their effects have been studied over the years in the field of relevant accidents of cell process and pleiotropic and non-toxicity for normal cells. Food material can be considered as one of the environmental factors responsible for 20-30% of colon cancer cases, since food materials can be considered as microenvironment determinant factors of colon cancer cells and the interactions between cancer cells and microenvironment around cell can also affect tumor growth (2).

Among chemoprevention factors decreasing risk of cancer, phytochemicals can be the most important factors (12-15). The majority of studies conducted over the 3 decades have introduced the materials extracted from plants as factor suppressing or creating delay in progression of types of cancers. The results are consistent with the findings of epidemiologic studies showing that using fruits and green and yellow vegetables can reduce cancer and mortality in colon, breast, prostate, esophagus and bladder cancers (14, 16, 17). Phytochemicals are non-nutritious herbal compounds with anti-cancer effects (18).

According to the book "Fundamentals of Cancer Prevention", cancer prevention happens in 3 steps: the first step (mainly prevention of carcinogens), second step (identification and elimination of benign lesions) and third step (prevention of cancer relapse, tumor progress)

Phytochemicals can have preventive effects in 3 steps against cancer from the beginning of tumor creation to all effective factors in cancer (cell proliferation, apoptosis, inflammation, genome stability) (11, 18).

As 2 main hallmarks of cancer cells are abnormal cell proliferation and resistance to apoptosis, identification of natural herbal edible components can be the most reliable compound (because of non-toxicity) to monitor cancer treatment (19, 20).

One of these compounds can be a natural substance (3, 4, and 5-trihydroxytrans-acetilin) with abundant biologic effects to prevent and treat cancer. A phytoalexin compound or antibiotic is the plant produced in the plant abundantly in response to environmental stress and pathologic attack and acts therefore as a natural prevention factor of cell proliferation (21, 22). The compound is produced from attachment of cinnamoyl radicals (two) (23). It has been identified in more than 70 plant species including grape, berries, plums, peanuts and pine (21). Over the decades, it has been found that it has wide range of pharmacologic properties. It seems that additional biochemical and molecular activities in this substance can cause effects in cancer and pre-cancer cells (11, 22).

The information has led to take numerous basic animal studies to investigate the potential effects as a cancer chemopreventor substance. Moreover, it also imitates calorie limitation and promotes health and interferes in the ageing process (22).

It has been reported that it can inhibit accumulation of Platelets and LDL Oxidation, Nitric Oxide Synthesis and vein expansion in vivo (19) and inhibition of proliferation of smooth muscle cells through reduction of Cyclin A gene expression (24). Moreover, the compound can suppress cancer cell growth (in vitro) (1) and reduction of tumor growth in animal models (13). Recent studies have shown that it can cause apoptosis induction in cancer cells through increasing P53 gene expression and reduction of Bcl-2 gene expression (26).

The proposed mechanisms for anti-cancer effects include cell death induction through Fas level regulation in cells producing extracellular apoptosis (27-29), increase in caspase activity (30, 31), decreased inflammation through suppression of gene regulation products with NFKB (31), decrease in production of proteins associated with cell cycle (Expression of cyquilin-dependent kinases E, Cdk4, cyquilin D1) (31, 32), increase in SIRT1 expression (gene relevant to decrease in expression of surviving, cell life cycle and slowing down the ageing process) (34) and wingless inhibition Wnt (35).

Another phytochemical is quercetin. Quercetin is the second obvious flavonoid in plant species and is available in fruits and the majority of vegetables (36) and can be considered as a cancer prevention compound. Cancer prevention effects of the compound can be attributed to antioxidant activity of quercetin, inhibition of carcinogen activating enzymes, regulation of intracellular signal transfer and interaction of quercetin with receptors and other proteins (37).

Among proposed anti-cancer molecular mechanisms, direct effect of quercetin on reduction of Cyp1A7 activity in colon cancer (playing a role in activation of carcinogens) (37) can be referred to. Also, one can refer to the effect on estrogen and inhibitory effects on expression and yield of androgenic receptors (a similar activity of phytoestrogens) (38), induction of apoptosis through the Mitochondrial path (activation of caspase 3 and 9), decrease in Bcl-xs/Bcl-xl ratio and increase in Bax (39), effect on DNA failure, Poly (ADP-ribose) Polymerase (PARP) failure and increase in Bax and effect on Bcl-2 level (anti-apoptosis) (39), decrease in synthesis of inflammatory cytokines and iNOS gene expression (40).

Quercetin and both polyphenoles are available in red grapes. It has been demonstrated that simultaneous use of quercetin and polyphenole can cause reduction of restinosis level (probably through inhibition of smooth muscle cell proliferation). Therefore, using a combination of quercetin and polyphenole has high potential in cancer control (41).

Moreover, quercetin can cause inhibition of sulfate process and increase biofeedback and ultimately, treatment competency through inhibition of sulfate. However, further studies are needed in this field (22).

It seems that among all mentioned mechanisms, apoptosis induction and cell proliferation inhibition can be the most important underlying mechanisms affecting anti-cancer activity of phytochemicals, since these factors can cause apoptosis induction in the field of cancer treatment (42).
Apoptosis or cell planned death is a normal regulated process of suicide enabling living things to preserve cells and eliminate unwanted cells threatening their survival.
It seems that apoptosis is useful physiologically, since cells with apoptosis are removed by Phagocytosis before losing cell plasma membrane permeability. In this mode, cells with apoptosis induction in macrophages (especially phagosomes) are declined without damaging adjacent tissues (43).

Apoptosis is regulated differently from distance. In the extracellular path, it happens through activating apoptosis death receptors and through changing permeability of mitochondrial membrane. Defect in apoptosis plays a key role in formation of tumors and creation of neoplasia and failure of its order can cause resistance to chemotherapy and radiotherapy and can ultimately increase metastasis.
Finally, both paths activate ultimately a family of proteases called caspases (Cysteinyl Asparatete Specihi Proteinase) (44). Caspases are members of the Cysteine protease family and play a key role in beginning and implementation phase of apoptosis.

More than 100 types of Substrates caspases have been identified to date and new substrates are regularly added to this list, which can be catalyzed by caspases. Substrates of the proteases include Lamine, Actin, Endonucleases,

DNA repairing proteins and finally transcription factors. Activation of caspases is mostly specified to apoptosis and determination of activity of caspases can be used to differentiate necrosis and apoptosis (45).

In addition to apoptosis induction, cell cycle cessation is a hopeful strategy for cancer prevention. Cell cycle includes 4 steps respectively including G1, S, G2 and M (46). Abundant factors and proteins in various positive or negative controlling points can regulate the cycle carefully. In case of the existence of ideal factors (e.g. quercetin), cancer cells in G1 are induced by apoptosis, otherwise; the process enters to phase S with activity of other passing mechanisms. With continuity of the ideal factors (like quercetin), with increase in cancer cell treatment time, apoptosis is induced. Cell proliferation plays a key role in multiple carcinogenic steps with genetic variations. Therefore, cell proliferation control is important for cancer prevention (46). Quercetin and other flavonoids can inhibit proliferation of colon cancer cells (1) and stomach cancer cells (43).

In addition to bromodeoxyuridine method Brdu in DNA and analysis of cell cycle protein analysis, the number of Argyrophilic Nucleolar Organiser Regions (AgNoRs) is used to evaluate cell proliferation in many organs such as colon mucosa (10). Recent studies have shown that using quercetin can lead to considerable decrease in number of tumors in the colon and can also prevent tumor creation in the colon of Min rats (13, 46, 47). It should be mentioned that cell proliferation changes in epithelial colon cell proliferation can increase risk of colon cancer.

Quercetin (48) and (47) can cause decrease in D1 and D2 cyclin gene expression, which can directly play a role in progress of the cell cycle and it has been also demonstrated that the substance has anti-cell proliferation effects and can make pauses in the cell cycle in vitro (20).

Analysis of the effect of quercetin in apoptosis induction, cell proliferation level and colon cell abnormalities is very important. Because of conflicting reports on effectiveness of quercetin in different steps of cancer (22, 24) and lack of studies investigating simultaneous effect of the two compounds on colon cancer in vivo; the present study tends to investigate the simultaneous effect of the two compounds, so that positive results obtained from the study can be generalized to human studies.

Positive effects created in inhibition of toxicity of Methotrexate can be attributed to antioxidant properties of quercetin, which can increase antioxidant capacity and can also decrease oxidative stress in cells. Antioxidant capacity of plasma in the second group was significantly reduced compared to the control group. However, antioxidant capacity of plasma was significantly increased in the group under treatment with quercetin. At the same time, it is decreased with serum tissue and kidney tissue of MDA and FRAP has been also increased. The process can be attributed to the presence of quercetin antioxidant (13). Moreover, in a study, Abdolvahab et al studied the effect of spinaciaoleracea on Methotrexate liver toxicity in rats and showed that decrease in ALT and MDA Methotrexate can increase glutathione. Treatment with extract of this plant can lead to Hepatobiliary disorders. Significant decrease in MDA was observed and the effect was associated with the antioxidant property of quercetin in spinaciaoleracea (36), which is consistent with histological results obtained from kidney tissue in this study. Moreover, in this study, the results of histopathologic studies of kidney and liver are consistent with biochemical tissues and confirm the findings (2, 3 and 4) (Figure 1). In this study, the results showed presence of severe lymphatic arthritis in kidney and liver tissue of the test group without treatment and getting just Methotrexate (Figures 3 and 4). However, prescription of quercetin can decrease lymphatic arthritis and generally, decrease damage. In the study on liver and kidney, the effect of quercetin, Rutin and allopurinol on uric acid level and kidney dysfunction caused by fructose intake in rats showed that the materials can decrease uric acid, urea, creatinine and decrease inflammatory cell infiltration in Crossbone tissue of the rat's kidney (37) and the findings are consistent with results of this study. However, it was observed in this study that serum concentration of urea in the second group (test group without treatment) showed significant decrease compared to the group getting silymarin (group 4) and had a liver protection antioxidant (26) and the effect was probably caused by liver damage by Methotrexate and as a result, decrease in urea synthesis in liver urea cycle, since in the group under treatment with silymarin, serum concentration of urea was almost close to serum level of the control group. In general, in this regard, one can refer to the studies conducted on quercetin, which showed that quercetin has anti-inflammatory, and antioxidant properties and also provides strong protection (15, 16, 18). Kidney and liver superoxide is an enzyme available in cytoplasm Cell Dismutase (SOD) and is also one of the defensive lines against free radicals and can protect tissues against active hydroxyl radicals (3). Quercetin is a penta-hydroxyl flavonoid in fruits and vegetables.

Foods like green and black tea, apple and onion are rich in quercetin with antioxidant and anti-inflammatory, antiviral and anti-cancer properties for a wide range of diseases (12, 14). It also has anti-cancer properties in ovarian, colon, intestine and breast cancers. Studies have shown that quercetin has anti-proliferation effect in cancer cells during inhibition of PKB/PI3K/Akt path (13). Quercetin can be used to treat AIDS, malaria, cardiovascular disease as well as cancer (10) and can induce apoptosis in breast cancer cells and prevent their growth (16, 19). Moreover, quercetin can inhibit Angiogenesis in tamoxifen-resistant Breast cancer (17). As different materials show their effect through affecting cell proliferation, to use the two materials, the effective dose and toxicity of the materials should be obtained in breast cancer cells above all. To this end, the amount of IC50 is determined as required dose to inhibit growth of 94% of cancer cells.

Conclusion

Curcuma longa is a type of plant from ginger and Yellow Chubs strain used for thousands of year for treatment of diseases such as cold, fever, skin diseases, liver diseases and stomachache and it is not toxic even in high doses. Curcumin (Di Ferrouilly Methane) is a Polyphenylene from Ariel Heptanoids strain and quercetin is also one of the flavonoids from flavonole strain and form the main compounds of yellow chub. The two substances have been considered as an effective compound to treat cancer. Some studies have confirmed significant correlation between diet of the two substances and reduced level of cardiovascular diseases and cancer and it can be used to make antibacterial, antiviral, anti-fungal and anti-tumor medicines. The two natural substances have anti-cancer properties. Various studies have been conducted to determine the treatment dose and to determine their IC50 on types of cancer cells (1-3). In this study, the percentage of survival and IC50 on breast cancer cells of 4T1 rats are determined. The results show that survival of cells in the control group has shown the highest level and the level is considered to be 100%. However, after 20 minutes and 8 hours contact with curcumin, the survival percent is reduced and the reduction has only depended on concentration. Regarding quercetin, at two times of 20 and 08 hours, it was found that reduction of survival percentage depended on both factors of concentration and time and with increase in both factors, the cell survival percent is reduced significantly. Regarding curcumin, the amount of IC50 at the time of 20 hours is equal to 10.8±4.0µg/ml and at 08 hours, it is equal to 21±4.3 µg/ml. Regarding quercetin, the amount of IC50 was equal to 21.7±4.7µg/ml at 20 hours and equal to 18.2±4.09µg/ml at 08 hours.

Feng Zhang et al investigated the effect of quercetin on HEN1 cells and showed that it can decrease cell proliferation and cell lifetime significantly (22). Vidya et al studied the toxicity of quercetin on Hela cells and mentioned that with increase in concentration and time, the lifetime of cells was decreased and IC50 was mentioned at 84µmol (23). Singhal determined IC50 at first to analyze the effect of quercetin on activity of enzymes in breast cancer cells MDA-MB-435 and showed that with increase in concentration, the inhibition percent is increased (20). As the IC50 curcumin and quercetin level is different for different cancer cells and because of high spread of breast cancer in Iran and closeness of 4T1 rat cell line to step 0 of human breast cancer, this study has used this cell line. In this study, toxicity of the two medicines on 4T1 cell strain is studied using MTT method and IC50 level is also determined for each of them. Moreover, the results obtained from this study showed that the percentage of survival for curcumin at 20 and 08 hours showed no significant difference; although for quercetin, with increase in time, the percentage is decreased significantly, so that the survival percentage at 20 hours is more than 08 hours.

The results obtained from this study showed that the survival of cells is dependent on concentration of curcumin and quercetin and the incubation time. With increase in solution concentration, the toxicity is increased and survival of cells at 08 hours has been decreased compared to at 20 hours.

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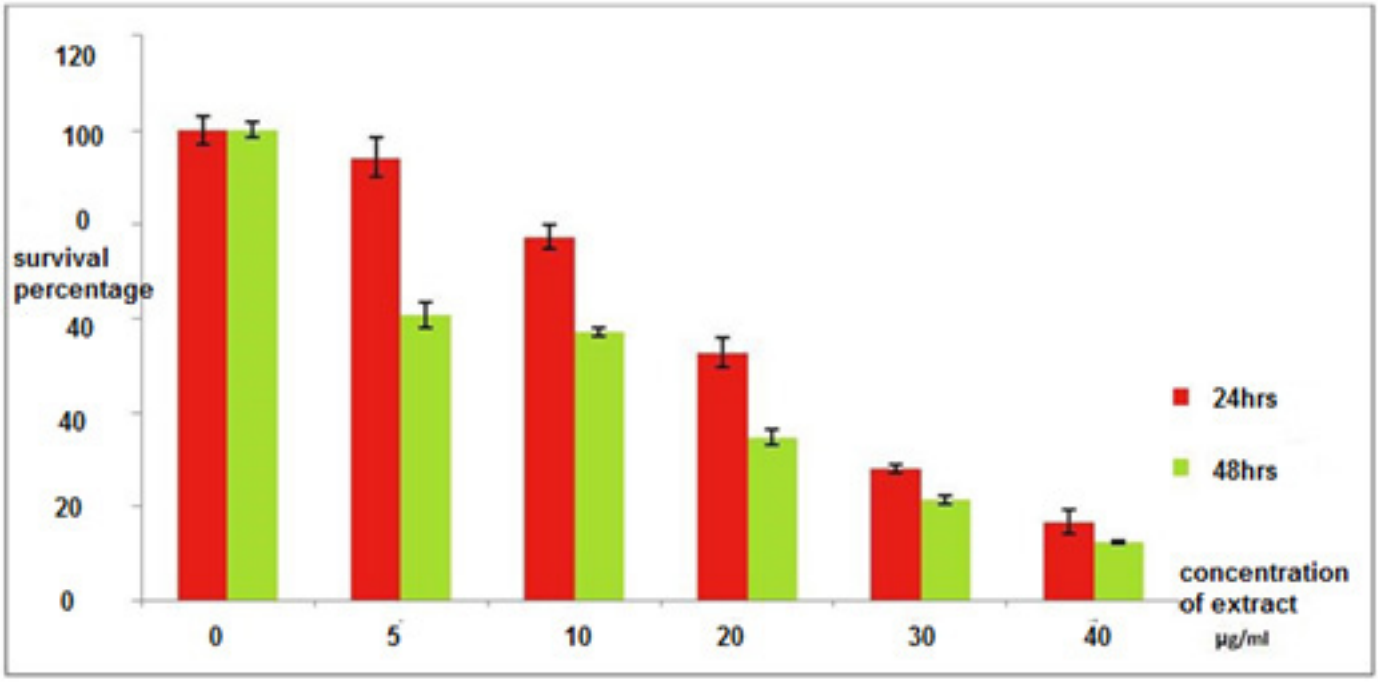
Figure 1: Cells survival percent in different concentrations of quercetin at 24 and 48 hours



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Evaluation of antimicrobial properties of derivative peptide of Naja naja snake's venom

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Abstract

Although most of the venoms and their derivative compounds have shown antimicrobial properties, most of them have not been studied to find such activities. In the world of pharmacology, along with invention and administration of new antibiotics, bacteria achieve new properties which allows them to become resistant to antibiotics; this proposes the issue of "antibiotic resistance", which motivates researchers to further study different natural resources in order to invent novel and effective antibiotics. Animal venoms have been in the center of attention because of their different observed effects, such as antibacterial effects. Venom is a very complex compound, consisting of different types of peptides and non-peptide materials with various activities. Few studies have been done to analyze antibacterial properties and purification of snake venoms. In this work, antibacterial effect of the derivative peptide of Cobra (Naja naja) snake against 4 bacteria (Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Pseudomonas aeruginosa) was studied and Minimal Inhibitory Concentration (MIC) was determined. At first, we quantified the intended dilution of lyophilized strains of bacteria and then diluted the peptide powder to the intended concentration. At first we added Mueller medium to all wells and then added peptide powder to the first well. We also added the provided concentration of bacteria to all of the wells. We evaluated light absorption using spectrophotometer after 16 hours of incubation at 37°C. Results of this analysis were compared to effects of 2 antibiotics (Ciprofloxacin and gentamycin). Results showed that the peptide derived from Naja snakes' venom has an antibacterial effect on gram-positive and gram-negative bacteria.

Key words: antimicrobial properties, peptide, Naja snake's venom

Introduction

Poisoning by snake venom is an important medical issue around the world and studying it is valuable. Millions of people get snakebite annually, and more than 100 thousand are killed by it. However, although snakebite is fatal, the venom has a natural biologic source that consists of compounds which have possible therapeutic values. Snake venom is a mixture of proteins, poly peptides, nucleotides, and non-organic compounds. Most of these proteins and poly peptides are in the monomer form, but those with complicated compounds show a high level of pharmacological activity [1].

Snake venom is used mainly for immobilizing and killing during hunting and it has a possible significance in defence. The fang is a shape shifted tooth of a snake, which has a groove (like an injection needle). In the viper family, fangs are bigger and are placed on the maxilla; they are moved by muscles, and while they are shorter in the Elapidae family such as cobras, they are constantly placed on maxilla. Hydrophis snakes have shorter fangs with some typical teeth on the maxilla [2, 3].

Semi-venomous snakes of the Colubrid family mostly have grooved fangs, which are placed at the posterior part of the maxilla. According to studies, a group of these peptides have shown good antimicrobial properties. These antimicrobial peptides (AMPs), which are generated by eukaryotes (e.g. mammals, amphibians, insects, and plants), are especially important because of their significant role in innate immunity. AMPs have a far-reaching activities against gram-positive and gram-negative bacteria, fungi, and viruses. They are also effective against multidrug resistant bacteria and have a low tendency to drug resistance [3]. Serious problems caused by multidrug resistant bacteria cause emergence of need for alternative therapeutics. AMPs are promising therapeutics as antimicrobial agents. Therefore, according to existing compounds in snake venoms, especially the cobra snake (Naja naja), studies in this field are essential so that we can use these derived compounds in the pharmacological and therapeutic fields [4-12].

Study Method

1. Growth mediums for identifying bacterium
Different mediums were used in this study, in order to identify bacteria, which have been mentioned below.

MacConkey agar growth medium
MacConkey agar growth medium consists of different compounds. These compounds are:

Table1: Constitutive compounds of agar growth medium.

No.	Compounds	Amount (gram)
1	Bacto-peptone	17
2	Proteose peptone	3
3	Baco lactose	10
4	Sodium chloride	5
5	Bacto-Bile Salt Mixture	1.5
6	Bacto-agar	13.5
7	Bacto-Neutral Red	0.03
8	Bacto-Crystal Violet	0.001

There are different instructions for preparing this medium. The instruction used to prepare this medium includes 50 grams in 1 liter of water. The intended amount of material is diluted in distilled water in an Erlenmeyer and then autoclaved. Mediums are divided into plates after becoming luke warm by heating. These plates then cross a flame so that the agar medium becomes solid. Plates are incubated at 37°C for 24 hours for the purpose of growing bacteria.

2. Triple sugar iron agar (TSI) medium
This medium is solid with light salmon and light brown granules, which becomes orange red by adding water to it.

Table 2: Constitutive compounds of TSI growth medium

No.	Compound	Amount (gram)	No.	Compound	Amount (gram)
1	Peptone from casein	10	7	D glucose	1
2	Peptone from meat	10	8	Ammonium iron citrate	0.5
3	Meat extract	3	9	Sodium thiosulfate	0.5
4	Yeast extract	3	10	Phenol red	0.024
5	Sodium chloride	5	11	Agar-agar	12
6	Sucrose	10	12	Lactose	10

The given instruction for preparing this medium is 56 grams in 1 liter of water. The intended amount of solid material is weighed and poured in an Erlenmeyer, then the required amount of distilled water is added. After that it is placed on a heater to boil. The liquid medium is divided into test tubes and then autoclaved. Tubes are placed obliquely so that a slant medium is obtained.

Using sterile microbiology loop once in order to culture bacteria in this medium, samples are picked up from colorless colonies on MacConkey medium and from colonies with black center on Salmonella-Shigella agar, are cultured deeply and are then taken out and cultured linearly on the slant. Cultured samples are incubated at 37°C for 12-24 hours.

3. Urea medium
Urea medium is prepared in two solid and liquid forms. Its compounds are shown in Table 2.3.

Table 3: Constitutive compounds of Urea culture medium

No.	Compounds	Amount (gram)
1	Yeast extract	0.1
2	Potassium dihydrogen phosphate	9.1
3	Di-sodium hydrogen phosphate	9.5
4	Urea	20
5	Phenol red	0.01

The given instructions from the company is 38.5 grams in 1 liter of distilled water and the medium should not be autoclaved. Small and narrow tubes are used to prepare a liquid medium. The intended number of small test tubes and distilled water are placed in an autoclave to be sterilized. The urea broth powder is dark purple before addition to water, while it becomes violet after being added to the water. The intended amount of the solid medium, which has been pre-weighed, is poured into an Erlenmeyer containing distilled water and then placed on a heater to be diluted. Then, the obtained liquid mediums are divided into tubes near the flame. Tubes are placed in a water containing beaker and then boiled in Bain Marie or on an alcohol burner for a 10 minute period. After cooling, the medium is available for being cultured. Samples are picked up from colorless colonies on the MacConkey agar and colonies with black center on Salmonella agar, using once, and then diluted in the liquid medium. The medium is incubated at 37°C for 12-24 hours. Urea positive samples in the urea broth medium turn the medium's color from light purple or pink into dark purple, while urea negative samples, such as Salmonella do not change the urea medium's color. In the solid urea medium, if the medium's color turns yellow, the urea is positive, and if it turns dark red or dark purple, the urea is negative.

Urease Test

The ability of a microorganism to synthesise from ammonium and CO2 can be found out by inoculating it to liquid and solid urea containing mediums. Microorganisms with the ability to synthesize this enzyme in large amounts can alkalinize the medium in a few hours; color changing will be apparent soon [58].

4. MR-VP (Methyl red-VoGes Proskauer) medium

This medium has bisque granules that turn orange by adding distilled water.

Table 4: Constitutive compounds of MR-VP culture medium

No.	Compound	Amount (gram)
1	Peptone from meat	1.7
2	D(+)glucose	2.5
3	Phosphate buffer	3.5

The given instruction by the company is 17 grams of medium in 1 liter of distilled water. After inoculation of bacteria in the medium and incubation at 37°C for 24 hours, 4-6 drops of alcoholic alpha-naphthol and 2 drops of KOH 40% are added to the tube per each drop of MR-VP medium. The tube is then shaken slightly so that oxygen reaches the culture medium. Existence of a red color on the surface of the medium indicates that the test is positive. This color usually appears 15-20 minutes after addition of barite indicator in the culture medium. Methyl red is added to the medium for MR test; red circle shows that the test is positive. MR-positive bacteria usually have negative VP and conversely, MR-negative bacteria usually have positive VP.

5. SIM medium

Table 5:

No.	Compound	Amount (gram)
1	Peptone from casein	20
2	Peptone from meat	6.6
3	Ammonium iron citrate	0.2
4	Sodium thiosulfate	0.2
5	Agar-agar	3

This medium is used with the purpose of analyzing production of H2S, production of indole, and motility in differentiation of enterobacter. The given instruction is 30 grams of medium in 1 liter of water. Samples are picked up from the culture using a sterile inoculating loop and then are inoculated deeply. If bacterium is immobile, its growth will happen along the inoculation line. H2S production is indicated by the medium's color turning black, where the bacterium has grown. In order to analyze indole production, the medium is coated with a layer of indole Co-Ax reagent. If indole has been produced, the indicator layer would turn violet.

6. SIM culture medium

This semisolid culture medium is used for recognizing three important properties of enterobacter (H2S production, indole production, and motility).

Hydrogen sulfide Production

A sterile inoculating loop is directly applied to the suspected colony; this is done by entering the colony for about 2CM and coming back in the same way. If microorganism can produce H2S, a black sediment will be observable in the medium.

Motility
Since the medium's agar concentration is low, if the bacterium is mobile, it will be able to move from the inoculated zone in all directions. If the medium becomes generally opaque, it indicates microorganism's motility. If microorganism is immobile, we will see an opaque part only in the track [13].

Indole production
Indole is the final product of metabolizing tryptophan amino acid, which is generated by tryptophanase enzyme's effect. After finishing incubation, some drops of Coax reagent, which has para-methyl aminobenzaldehyde in it, is added to the SIM culture media. If a red color exists, it will be formed constantly on the surface of the medium. Coax reagent is colorless; therefore, if test result is negative, it will not change in color [13].

EMB (Eosin methylene Blue Lactose Agar) culture media
The Eosin methylene blue medium is a culture medium which is used to insulate intestinal pathogenic basils, where their colonies are different from those that do not ferment lactose or sucrose. Some of the general types form mucoid colonies. Gram-positive bacteria do not grow on this medium due to existence of reagents; therefore, it's a selective medium. Identifying E.coli on this medium is available with small colonies and metallic polish. This bacterium's colonies are observed with a diameter of 2-3mm with a dark center [13]

Simmons Citrate Agar test
This medium contains cations, buffer, salt, citrate, and bromothymol blue as reagent, and the general color of it is green. The suspected microorganism colony is cultured on the surface, because the reaction needs oxygen. If the microorganism is able to metabolize citrate as a carbon source, the medium's color turns blue due to existence of bromothymol blue, and therefore, the test result is considered as positive. If the medium's color remains green, it means that the citrate has not been metabolized and PH has not changed; therefore, thetest result is negative [13].

Table 6: Biochemistry properties of E. coli

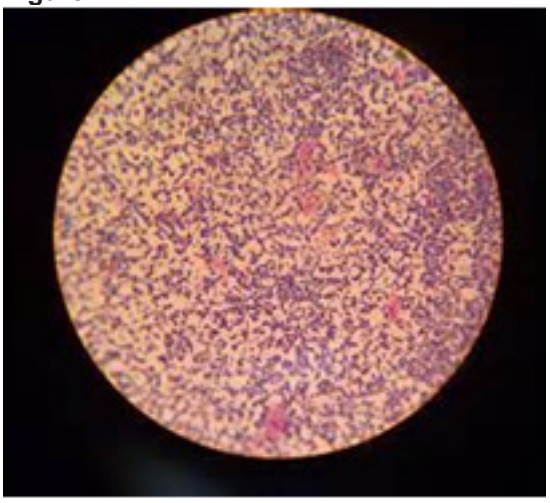
Test	Result
Indole	+
Methyl red	+
VP	-
Simmons Citrate	-
H_2S production in TSI	- (Except for some strains)

Blood agar culture medium
This is an enrichment media, which is used for proliferation and insulation of pathogenic bacteria, especially those that need nutrients for growing. In addition, existence of hemolysin in bacteria can be analyzed too. After autoclaving the basic medium, defibrinated blood of sheep is added to it with a ratio of 5 to 7; once its temperature reaches 50°C; then they are divided into sterile plates with a sterile condition [13].

Results

1. Gram staining
Staphylococcus aureus: Staphylococcus aureus was observed as a gram-positive (in purple) clustered cocci in gram staining.

Figure 1

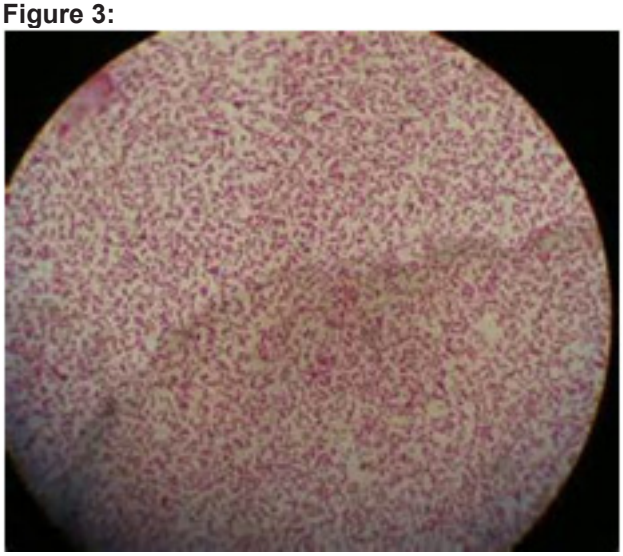


Bacillus subtilis: This is a gram-positive (in purple) basil, with approximate diameter of 1µ and length of 3-4µ.

Figure 2:

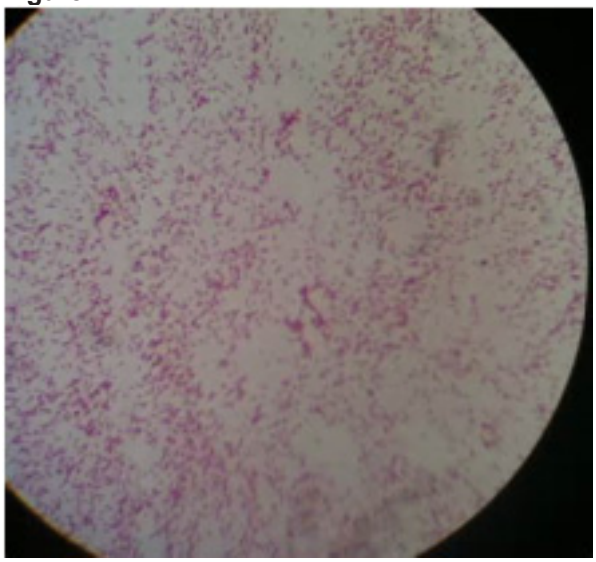
E.coli: These are gram-negative (in red) sporeless bacteria. Some have capsules. Their difference to enterobacteria is their size (which is usually 1.1-1.6 × 2-6µ).

Figure 3:



Pseudomonas aeruginosa: These are gram-negative (in red) bacteria with the size of 0.5-1µ × 3-4µ, which are formed as single, binary and sometimes, small chains.

Figure 4:



Dedicated tests for identifying each bacterium was done after gram staining.

2. Analysis of dedicated biochemistry tests' results
Staphylococcus aureus: It generated beta hemolysis on blood agar culture medium. After 24 hours, spherical, convex, smooth, and regular margin colonies with size of 1-4 mm were generated.

Figure 5:

It is capable of fermenting mannitol sugar on agar mannitol salt medium, which turns its red color to yellow. Catalase and coagulase tests were positive for Staphylococcus aureus.

Bacillus subtilis: Colonies have a relatively big size (about 3-4mm) in blood agar culture media. Catalase and gelatin were positive.

E.coli: Results of Escherichia coli culture showed that this bacterium is indole positive, MR positive, VP negative, and citrate positive.

Pseudomonas aeruginosa: Pseudomonas aeruginosa results in generation of beta hemolysis on blood agar medium and generates flat and thin edged colonies with size of 3-5 mm after 24 hours. Its oxidase test was positive and biochemistry tests verified it.

3. Analyzing effect of different concentrations of peptide on aforementioned bacteria
Light absorbance of different samples were read by spectrophotometer machine and the following diagrams show their results.

As Diagram 1 shows, the studied peptide has shown antibacterial properties for Staphylococcus aureus at wavelength of 600nm and concentrations until 150µg.

As Diagram 2 shows, the studied peptide has shown antibacterial properties for Bacillus subtilis at wavelength of 600nm and concentrations ≤ 150µg.

Diagram 1: comparing light absorbance in different concentrations by (µg) in wavelength of 600nm for Staphylococcus aureus.

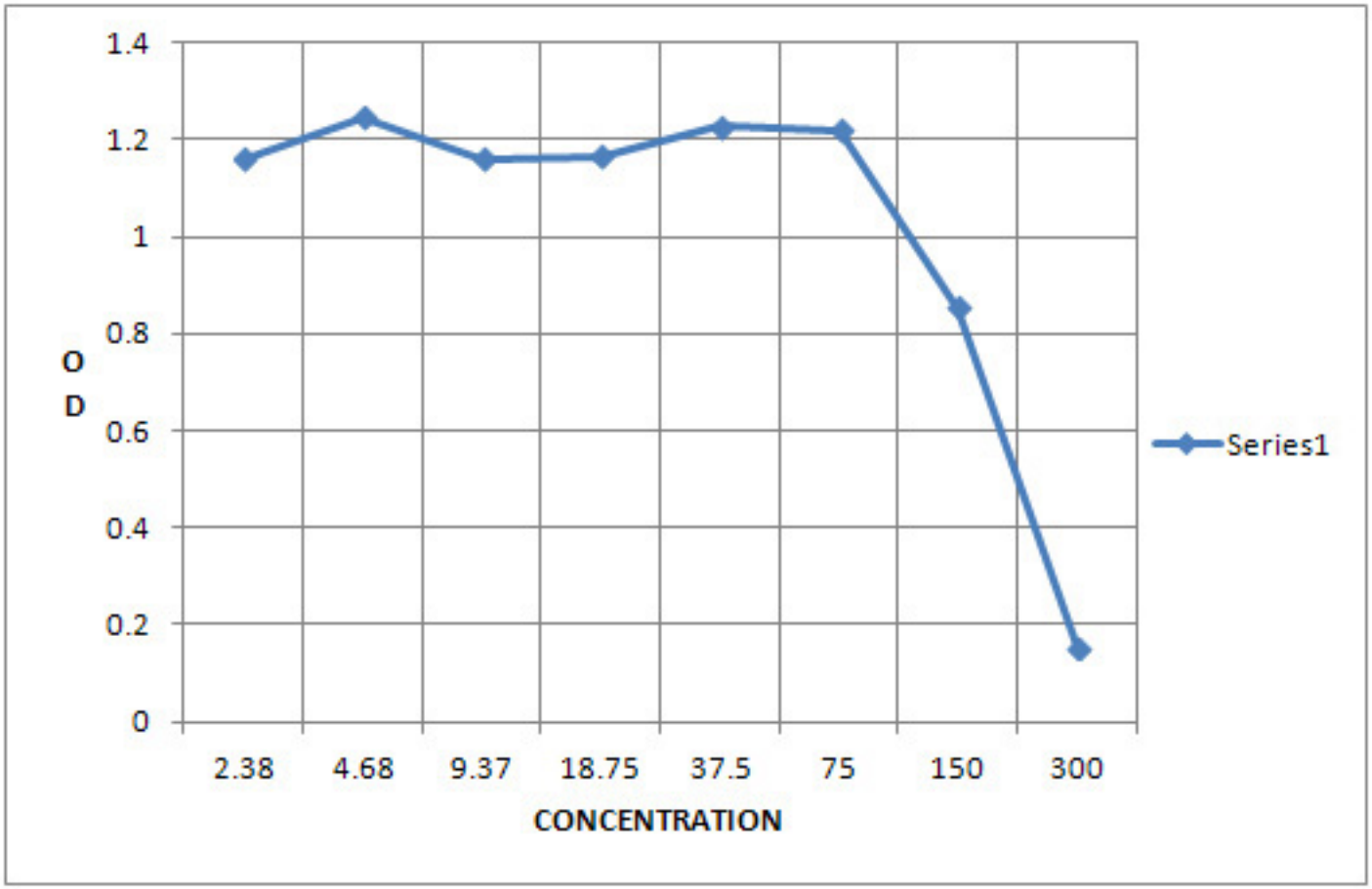
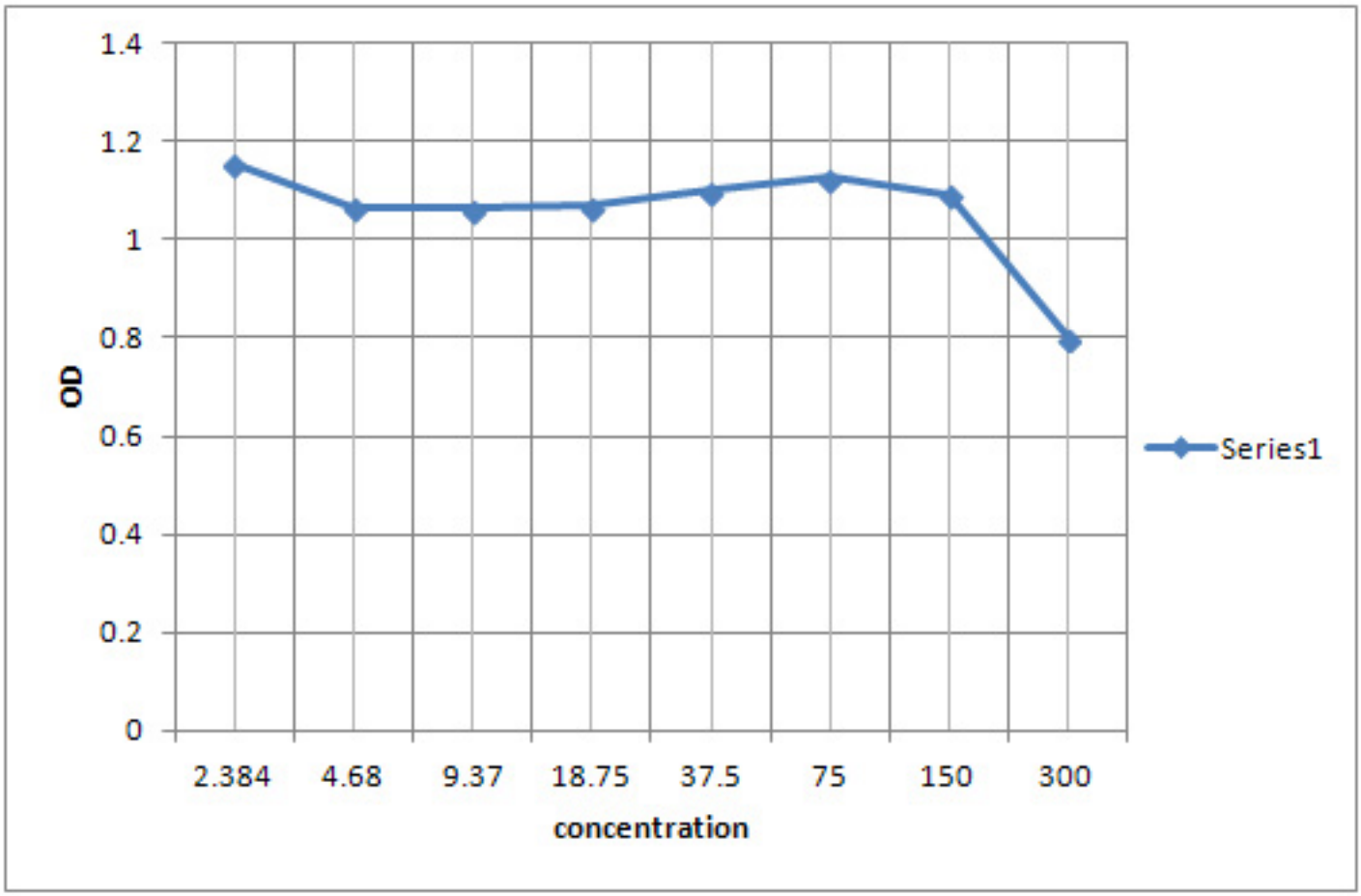
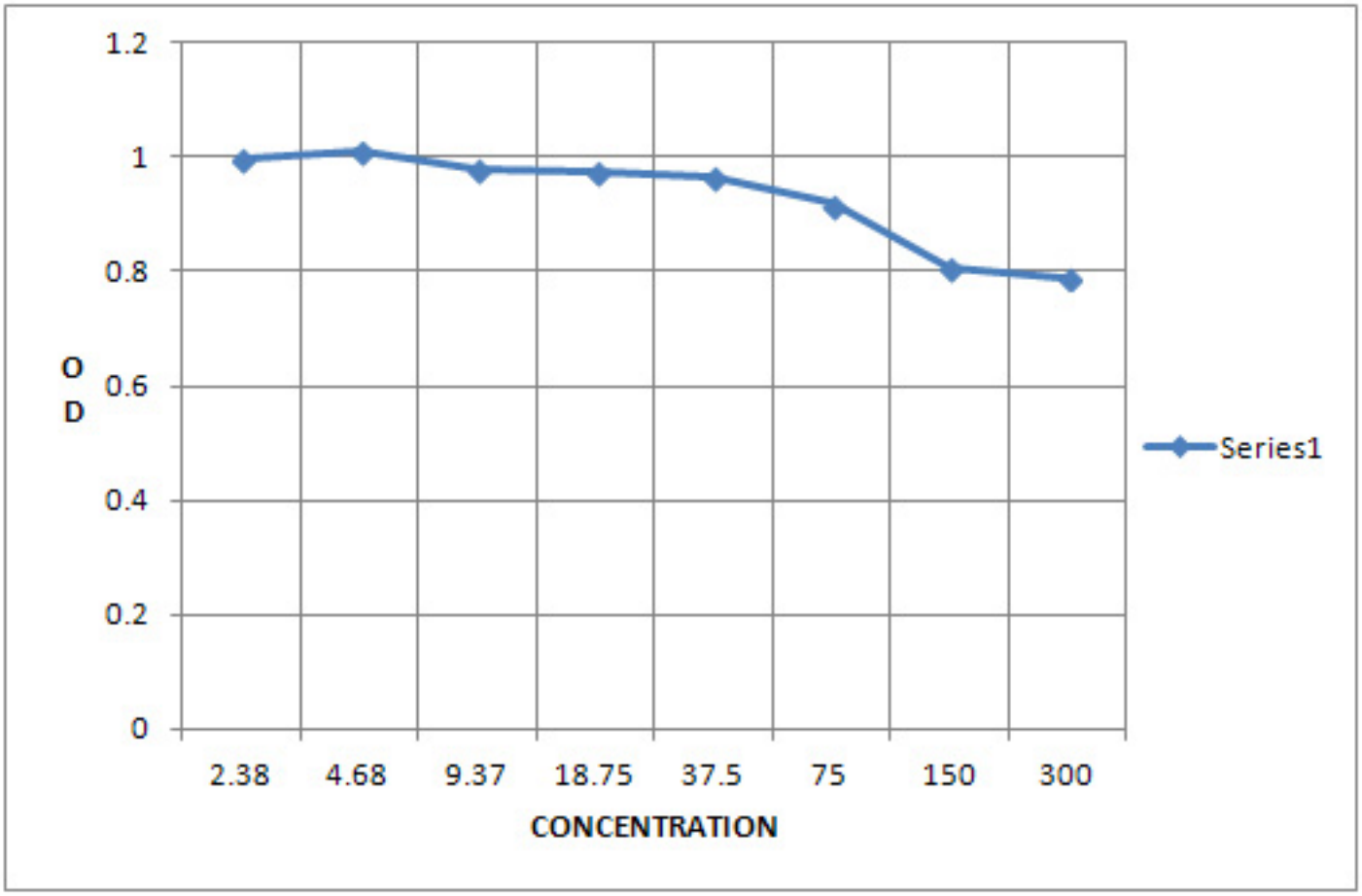


Diagram 2: comparing light absorbance in different concentrations by (µg) in wavelength of 600nm for Bacillus subtilis



As Diagram 3 shows, the studied peptide has shown antibacterial properties for E.coli at wavelength of 600nm and concentrations ≤ 75µg.

Diagram 3: comparing light absorbance in different concentrations by (µg) in wavelength of 600nm for E.coli.



As Diagram 4 shows, the studied peptide has shown antibacterial properties for Pseudomonas aeruginosa at wavelength of 600nm and concentrations ≤ 75µg.

We analyzed results once more at wavelength of 620nm:

As Diagram 5 shows, the studied peptide has shown antibacterial properties for Staphylococcus aureus at wavelength of 620nm and concentrations until 150µg.

Diagram 4: comparing light absorbance in different concentrations by (µg) in wavelength of 600nm for Pseudomonas aeruginosa.

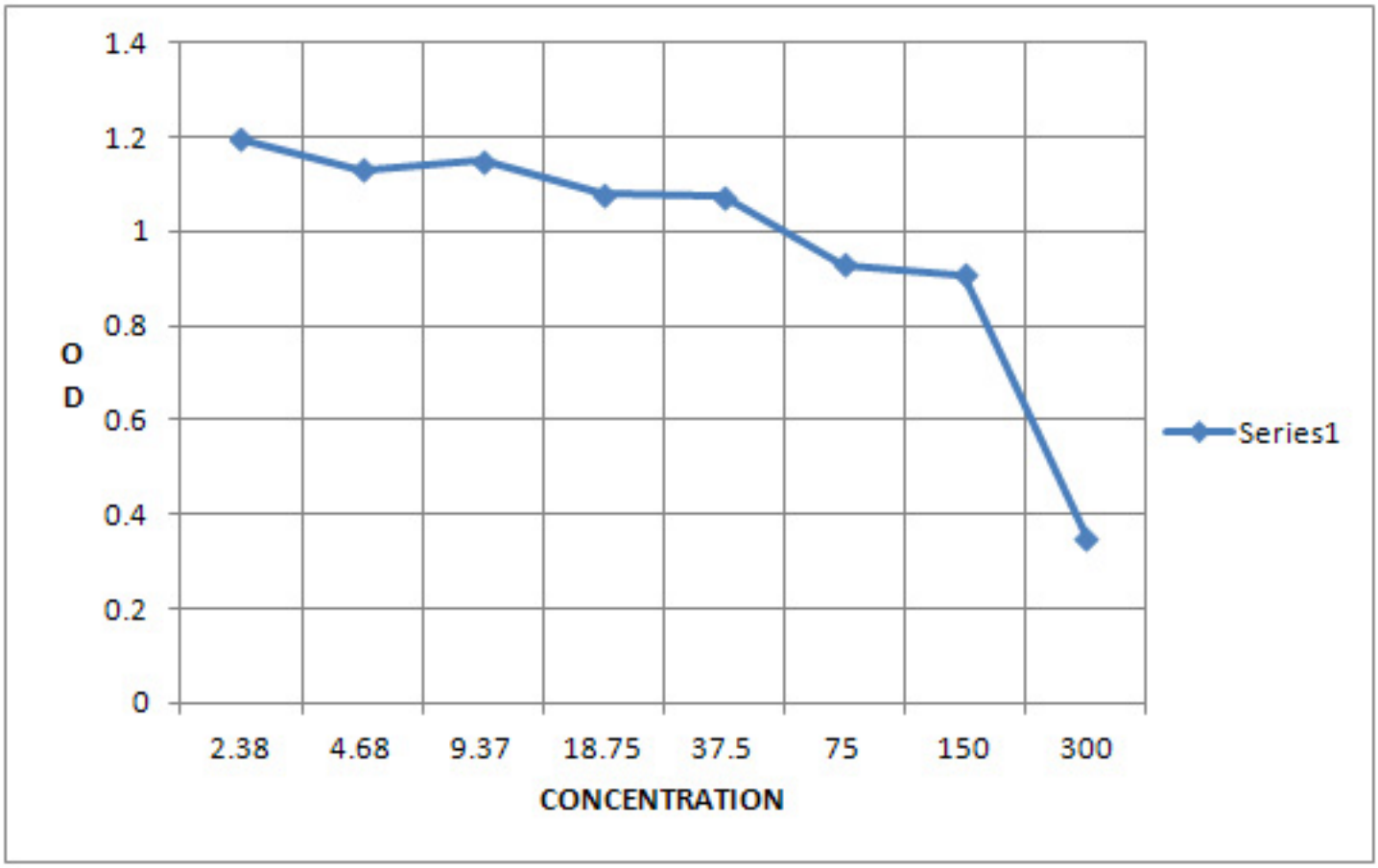
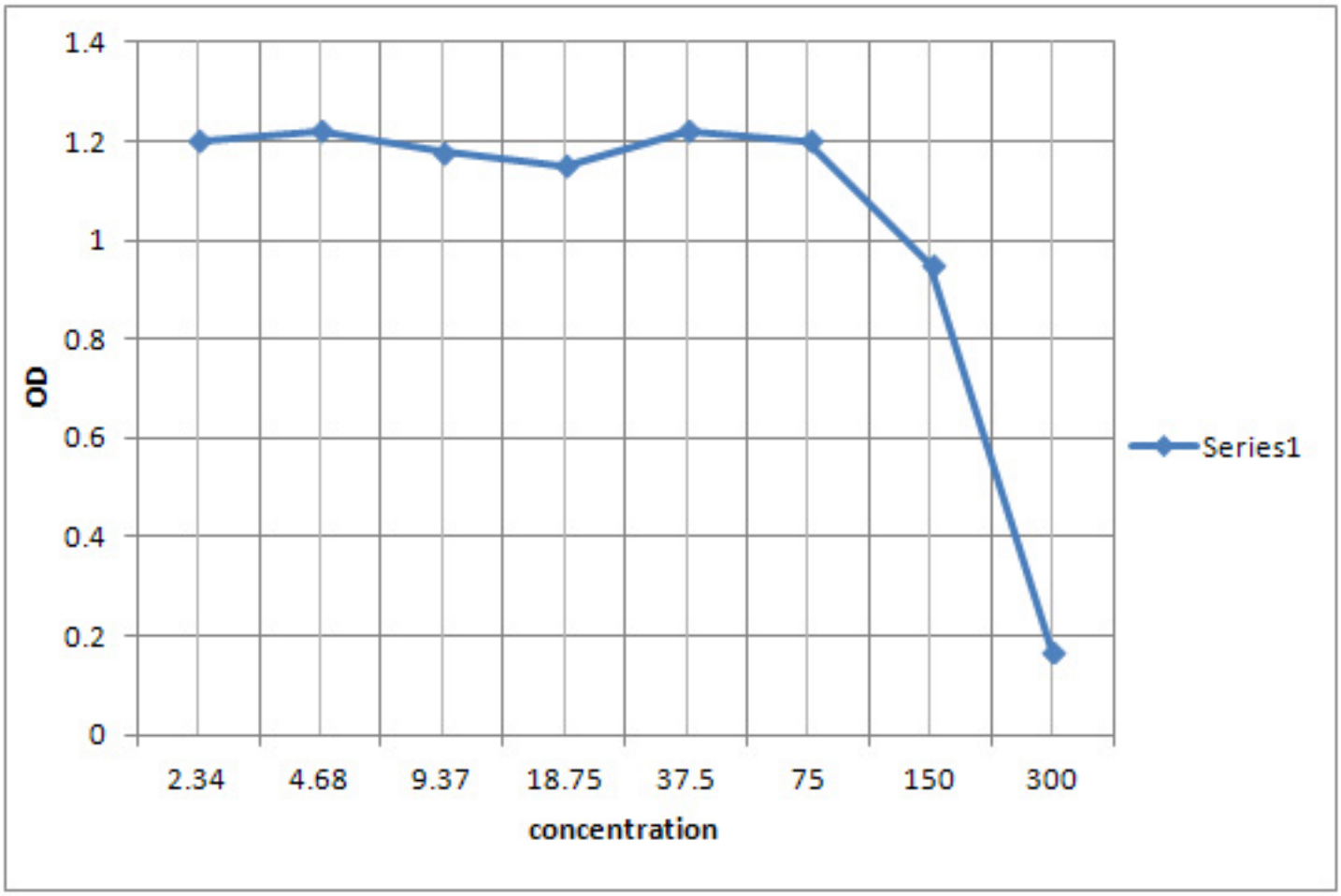
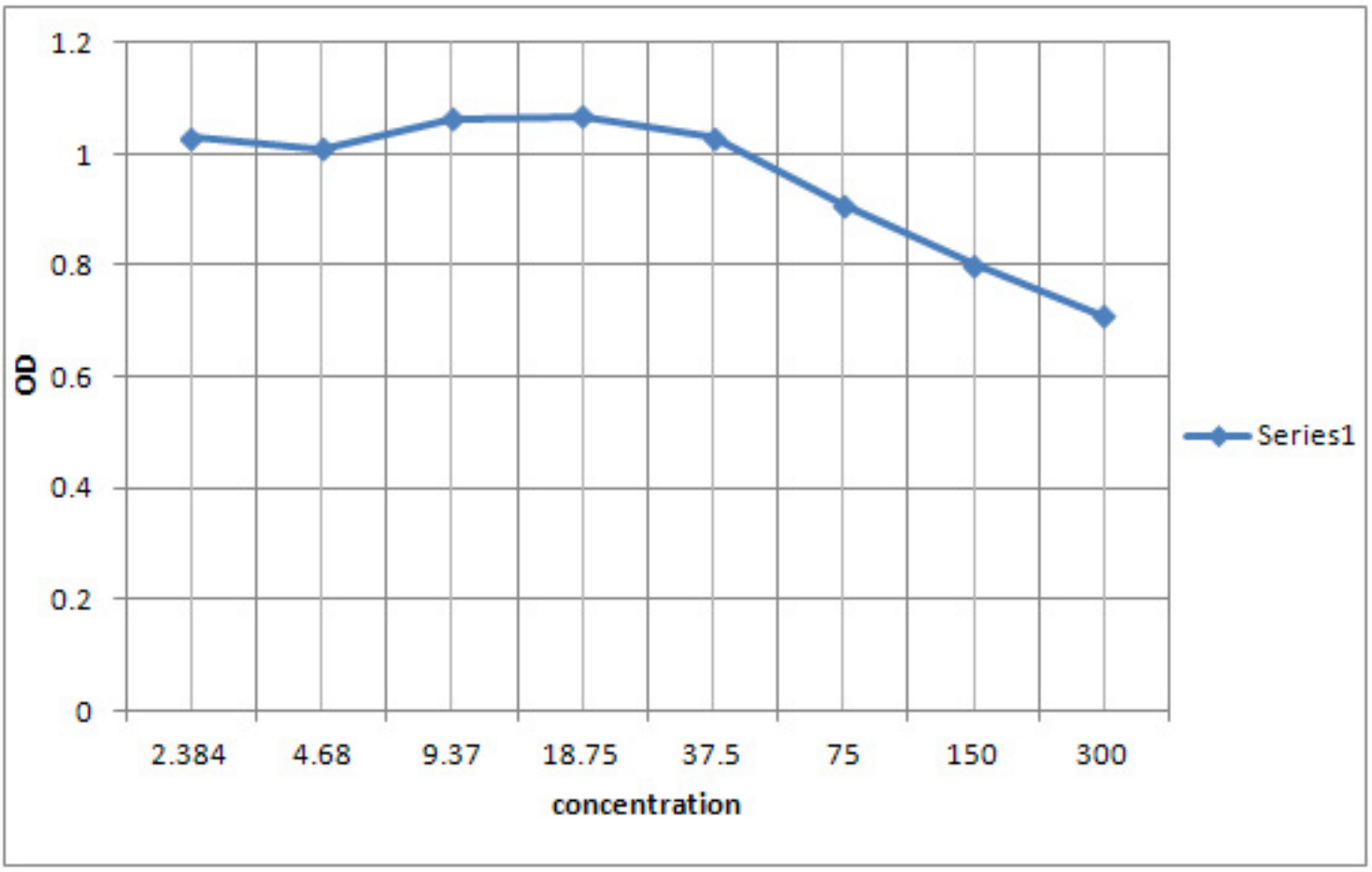


Diagram 5: comparing light absorbance in different concentrations by (µg) in wavelength of 620nm for Staphylococcus aureus.



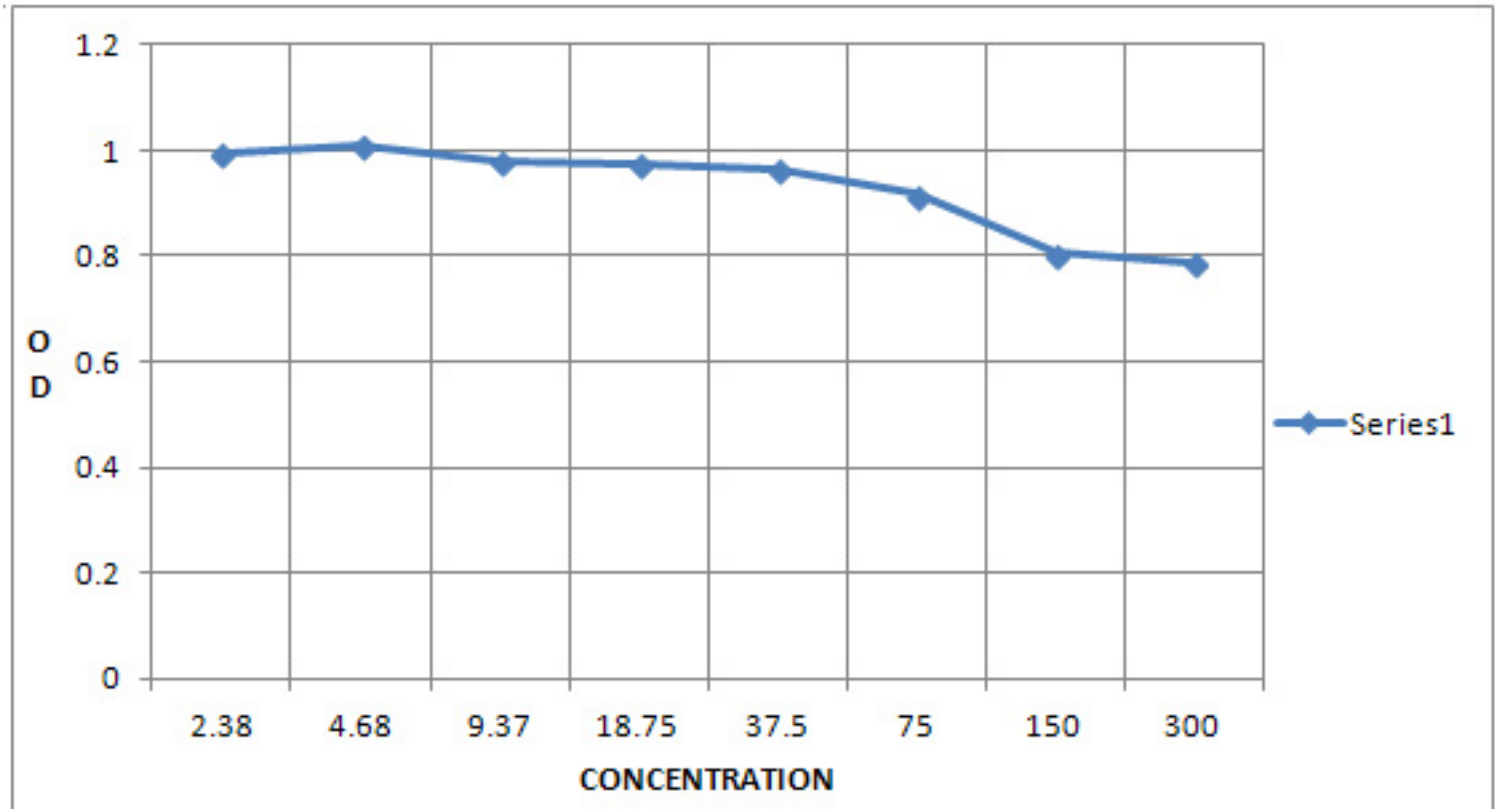
As Diagram 6 shows, the studied peptide has shown antibacterial properties for Bacillus subtilis at wavelength of 620nm and concentrations ≤ 150µg.

Diagram 6 comparing light absorbance in different concentrations by (µg) in wavelength of 620nm for Bacillus subtilis.



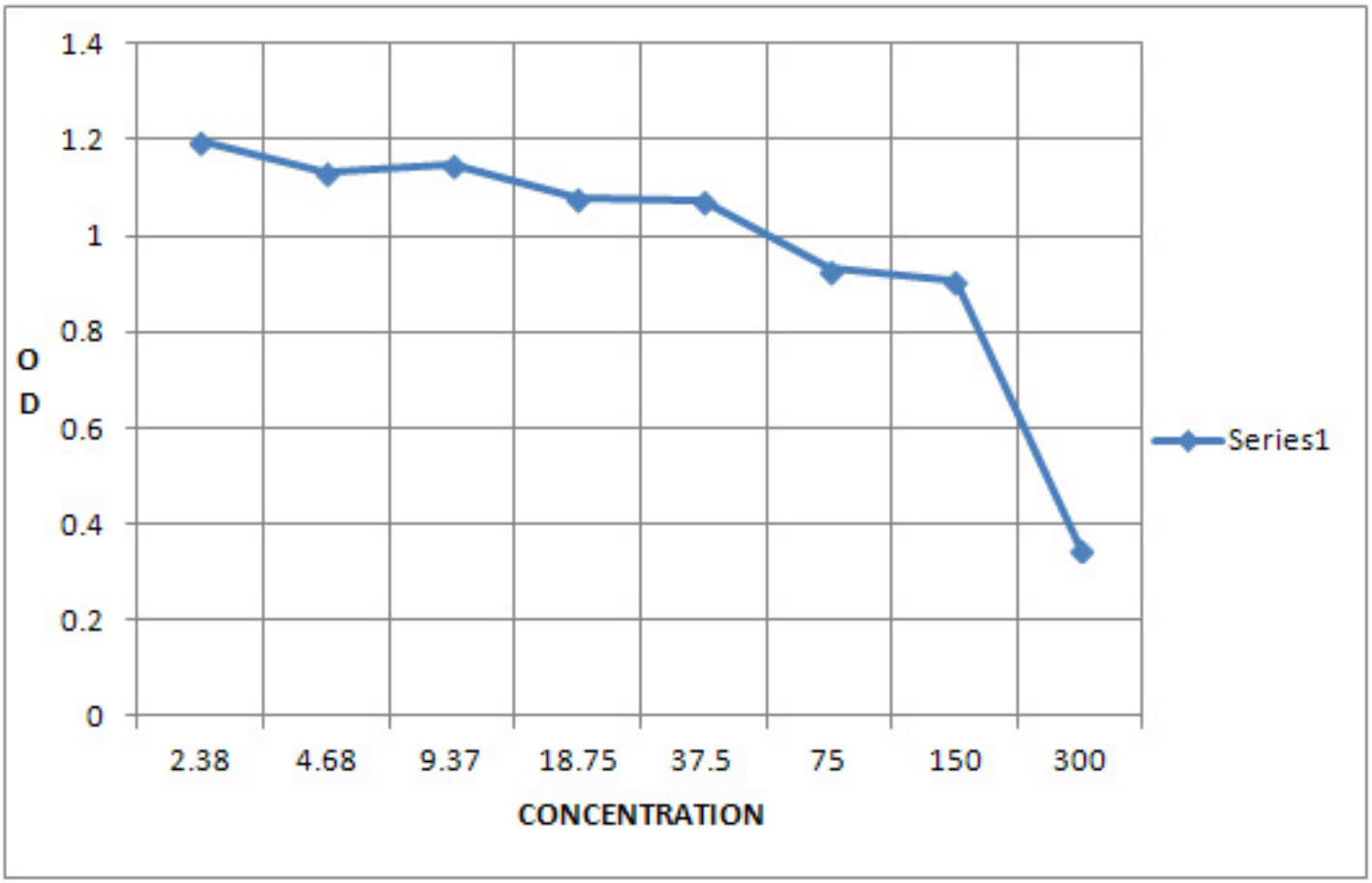
As Diagram 7 shows, the studied peptide has shown antibacterial properties for E. coli at wavelength of 620nm and concentrations ≤ 75µg**.**

Diagram 7: comparing light absorbance in different concentrations by (µg) in wavelength of 620nm for E. coli.



As Diagram 8 shows, the studied peptide has shown antibacterial properties for Pseudomonas aeruginosa at wavelength of 620nm and concentrations ≤ 75µg.

Diagram 8: comparing light absorbance in different concentrations by (µg) in wavelength of 620nm for Pseudomonas aeruginosa.



We studied minimal inhibitory concentrations at concentrations above 400, 500, and 600 except for 300. Obtained results are as follows (next page):

Diagram 9: comparing light absorbance in different concentrations by (µg) in wavelength of 620nm for Staphylococcus aureus.

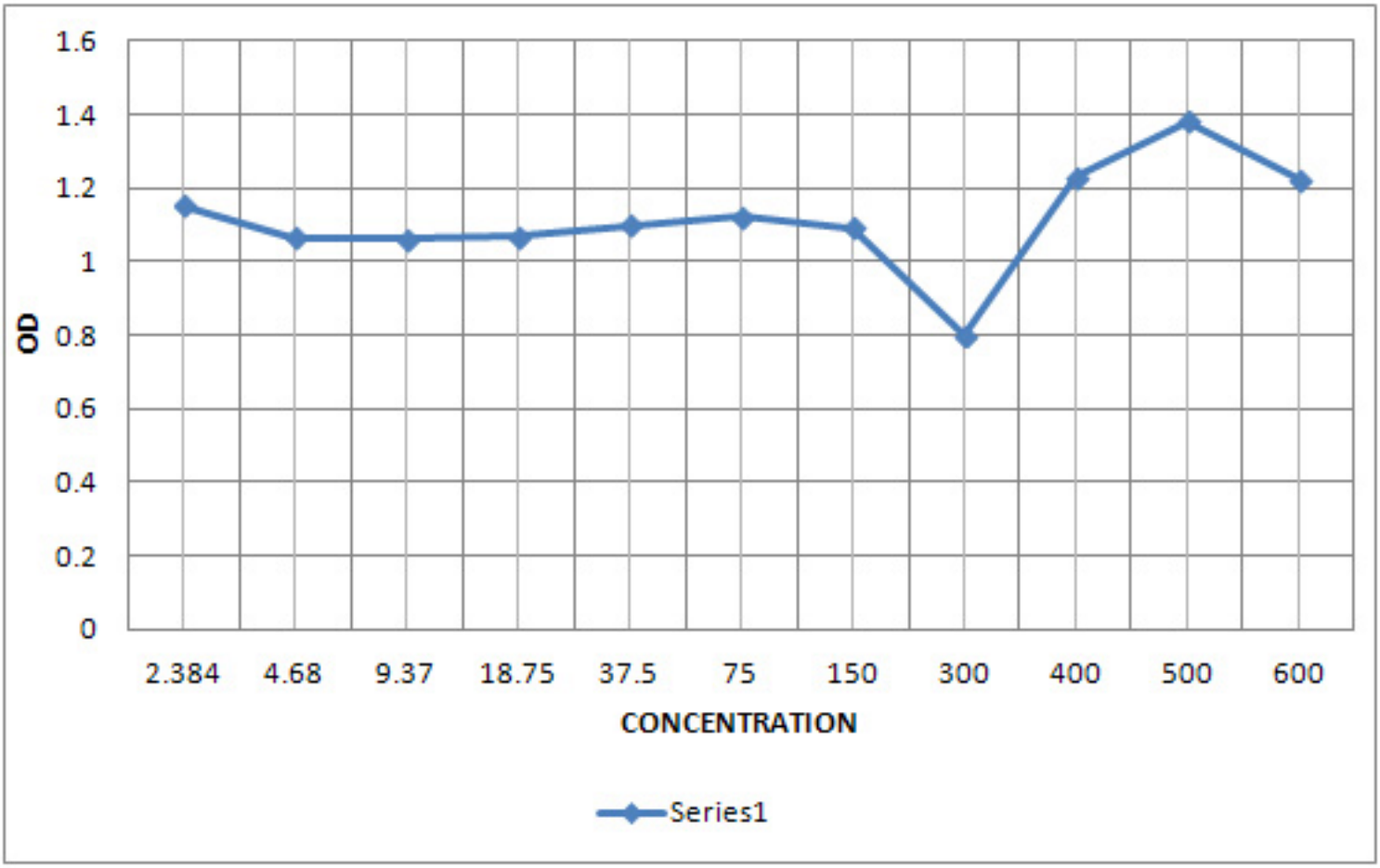


Diagram 10: comparing light absorbance in different concentrations by (µg) in wavelength of 620nm for Bacillus subtilis

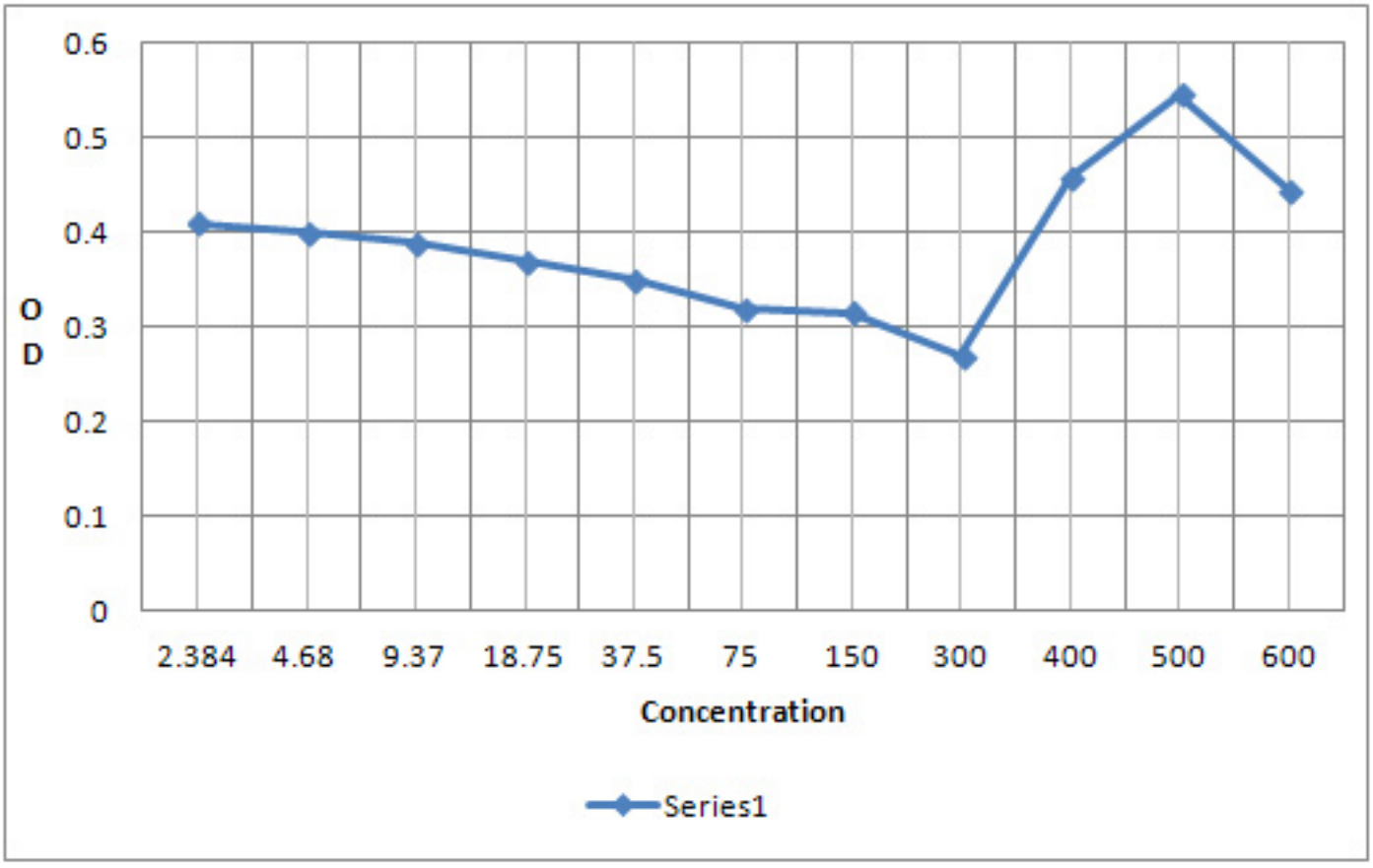


Diagram 11: comparing light absorbance in different concentrations by (µg) in wavelength of 620nm for E. coli.

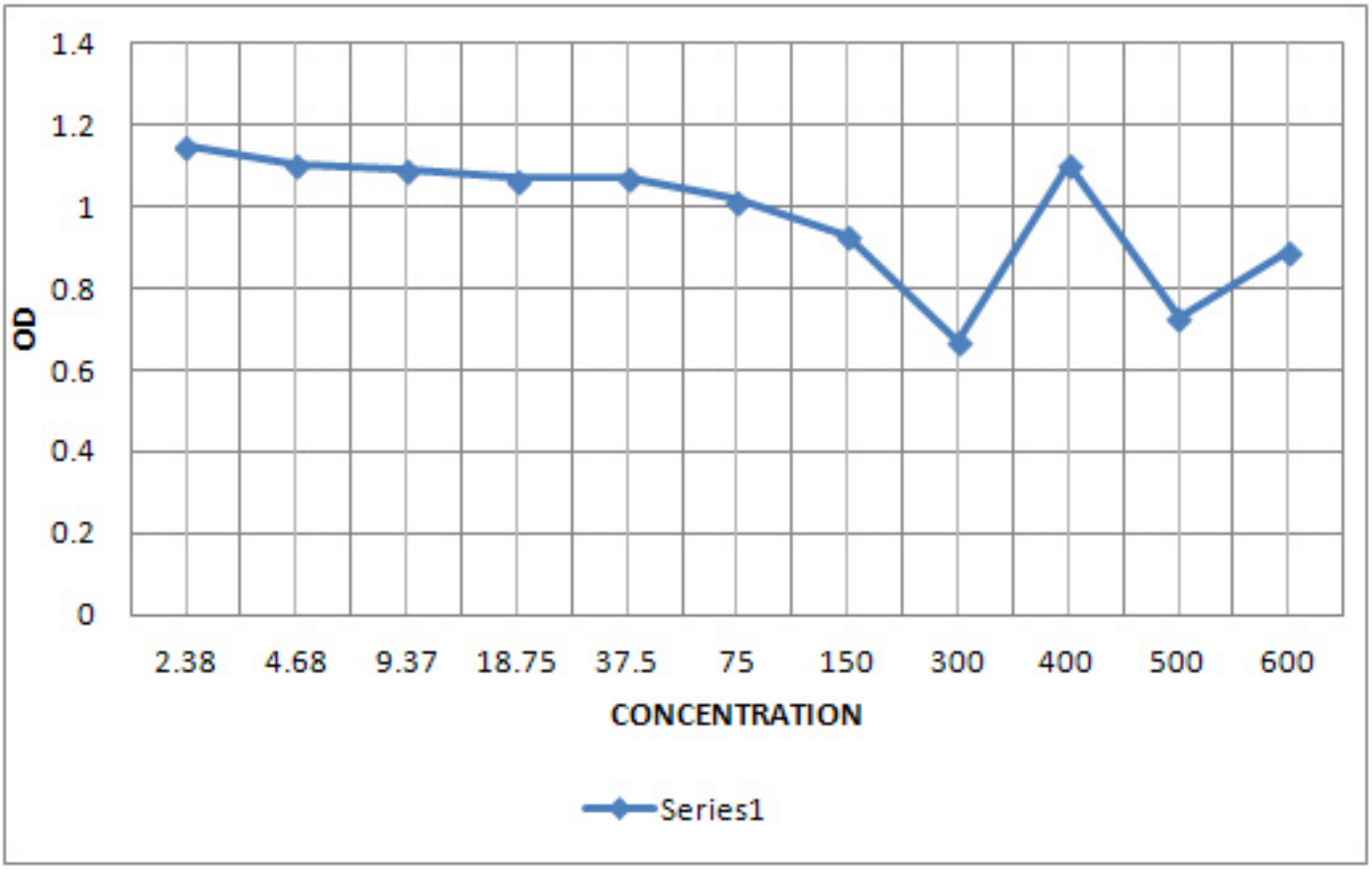
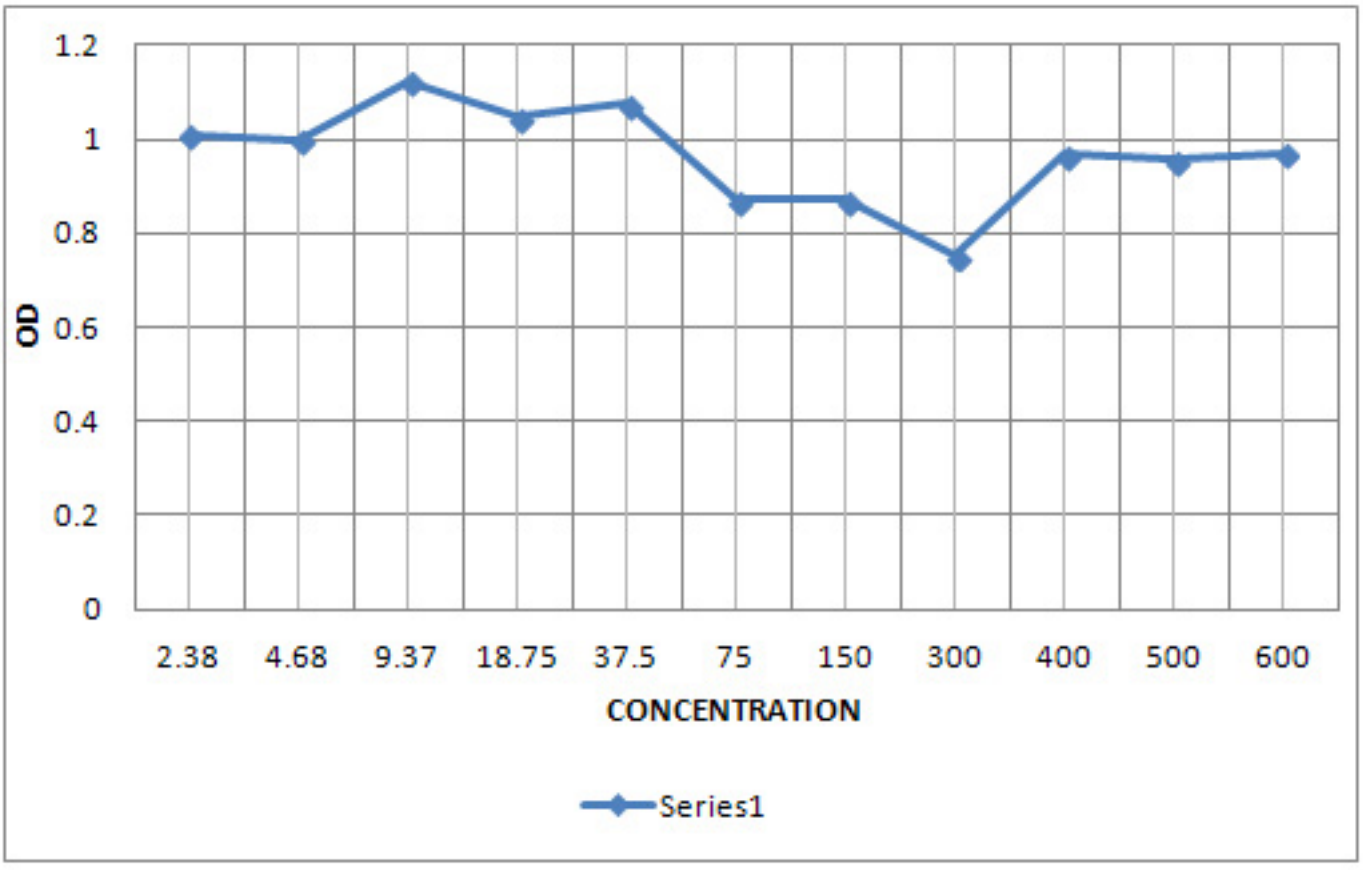


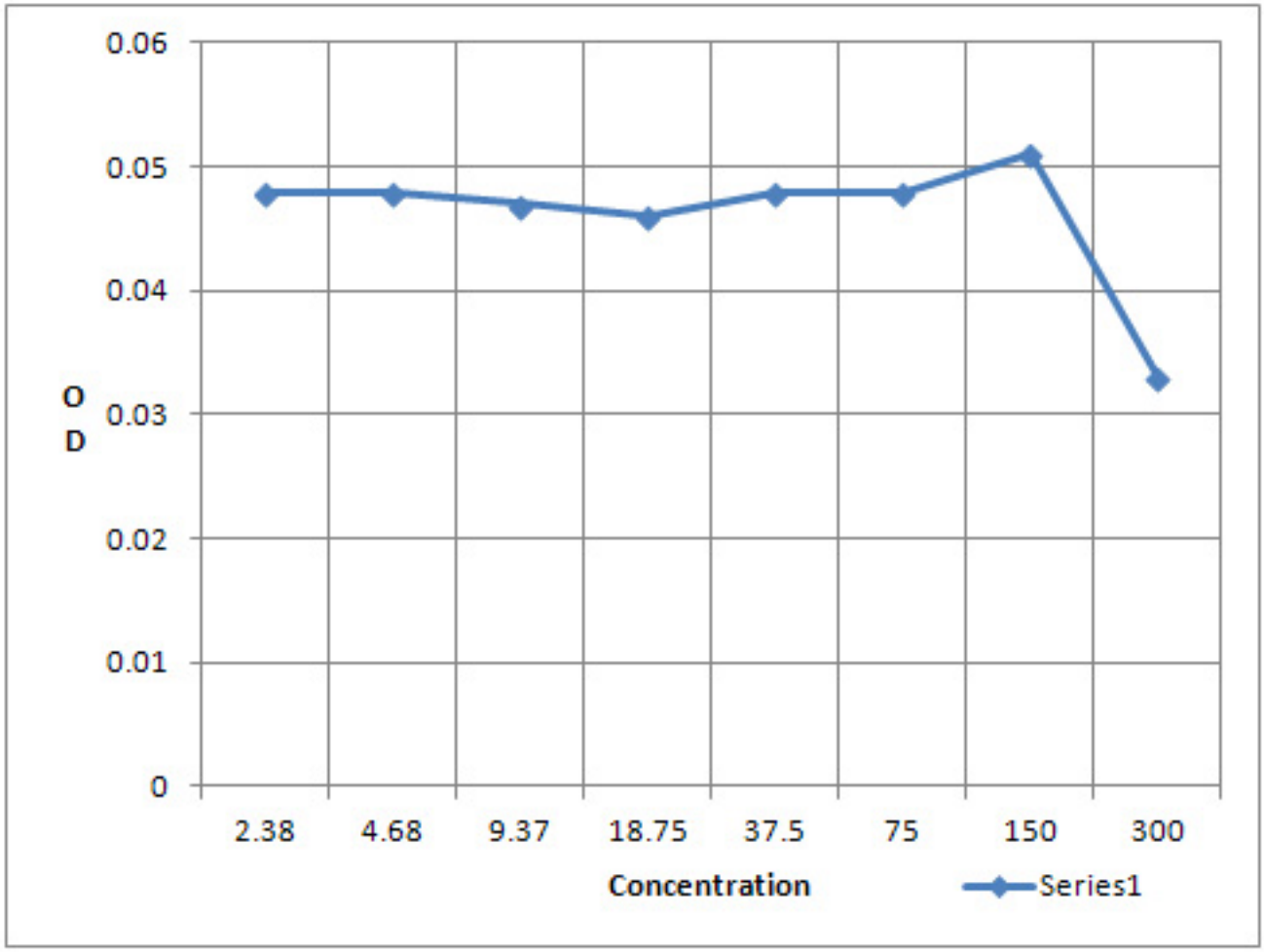
Diagram 12: comparing light absorbance in different concentrations by (µg) in wavelength of 620nm for Pseudomonas aeruginosa



We found out that the analyzed peptide does not show antimicrobial properties at concentrations more than 300µg. We compared results obtained from different concentrations of peptide to results obtained from antibiotic's effect, to see how much antibacterial effect the peptide has.

As you see in Diagram 13, antibiotic has shown antimicrobial properties at concentration of 300µg.

Diagram 13: comparing light absorbance in different concentrations by (µg) in wavelength of 600nm for Staphylococcus aureus



As you see in Diagram 14, antibiotic has shown antimicrobial properties at concentration of 300µg.

As you see in Diagram 15, antibiotic has shown antimicrobial properties at concentration of 300µg

Diagram 14 comparing light absorbance in different concentrations by (µg) in wavelength of 600nm for Bacillus subtilis

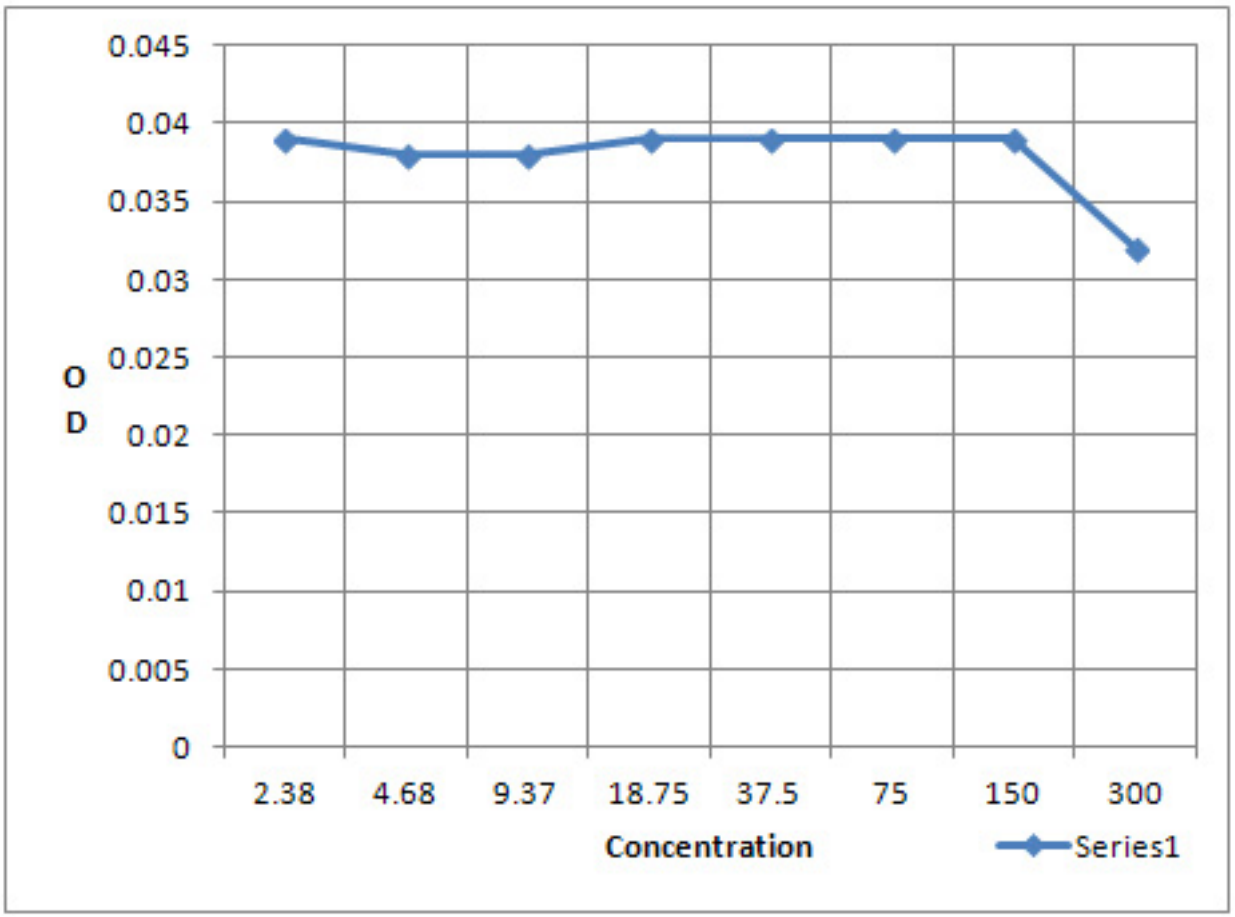
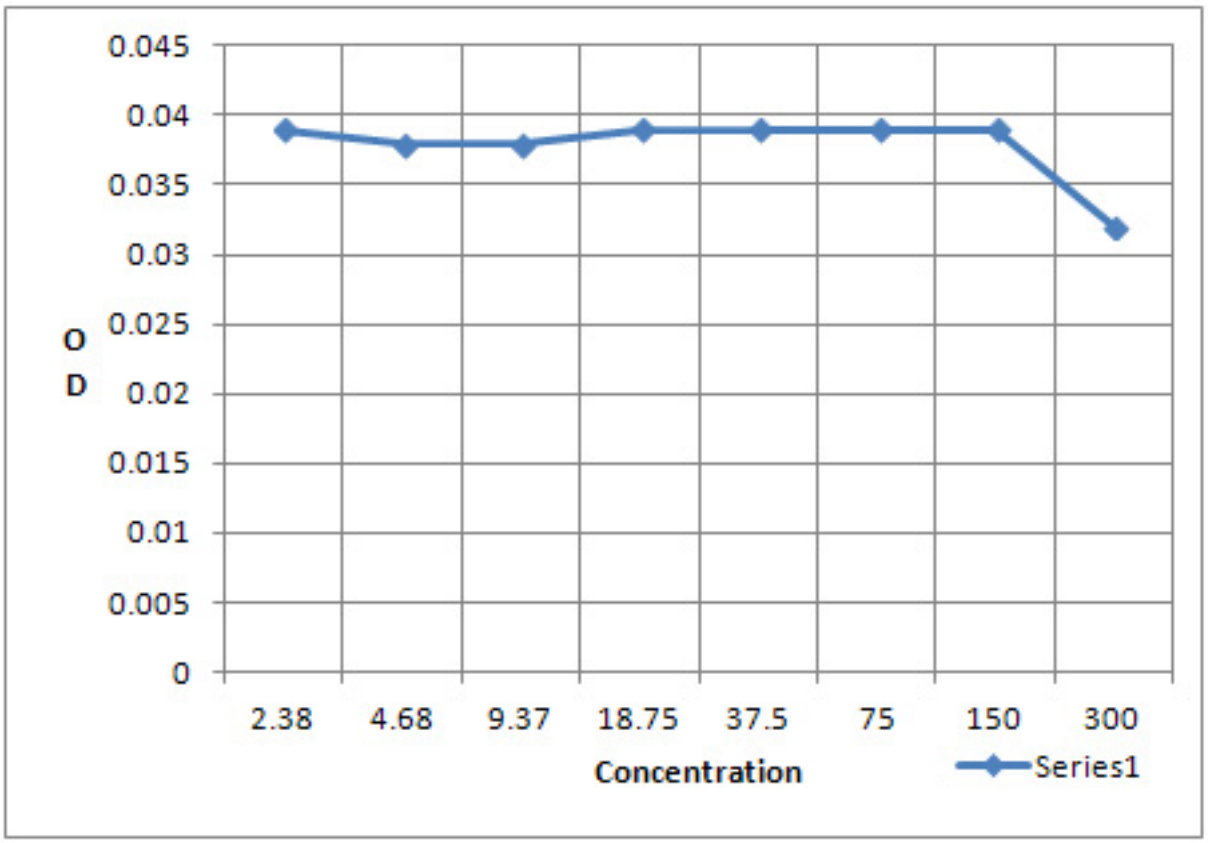
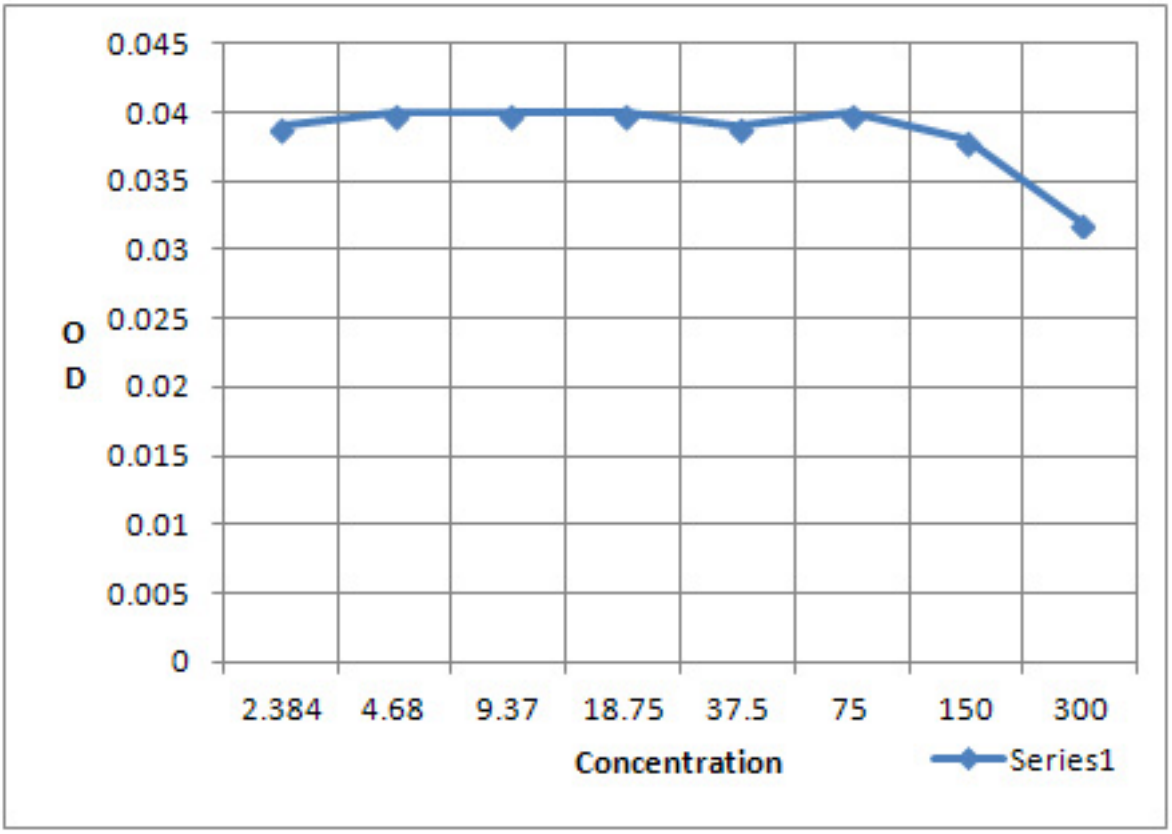


Diagram 15: comparing light absorbance in different concentrations by (µg) in wavelength of 600nm for E. coli.



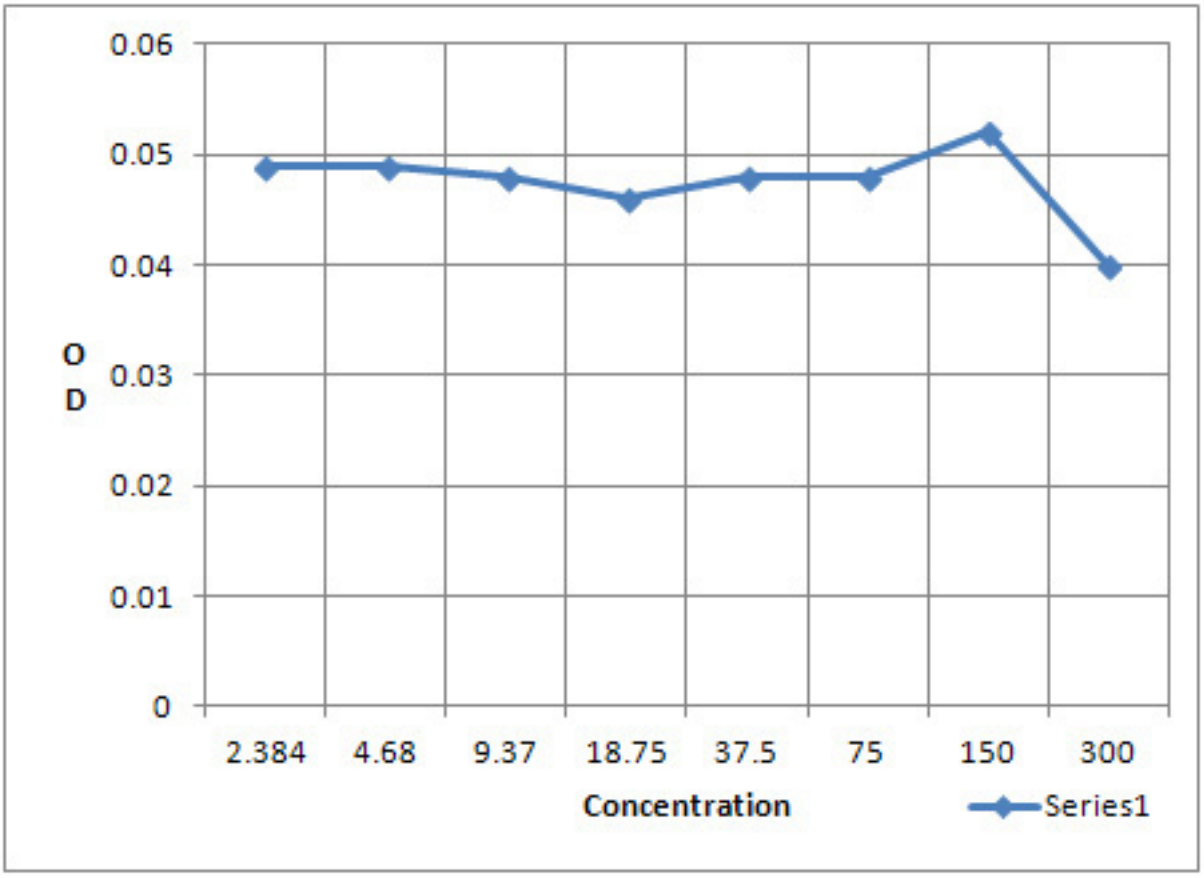
As you see in Diagram16, antibiotic has shown antimicrobial properties at concentration of 300µg.

Diagram 16: comparing light absorbance in different concentrations by (µg) in wavelength of 600nm for Pseudomonas aeruginosa



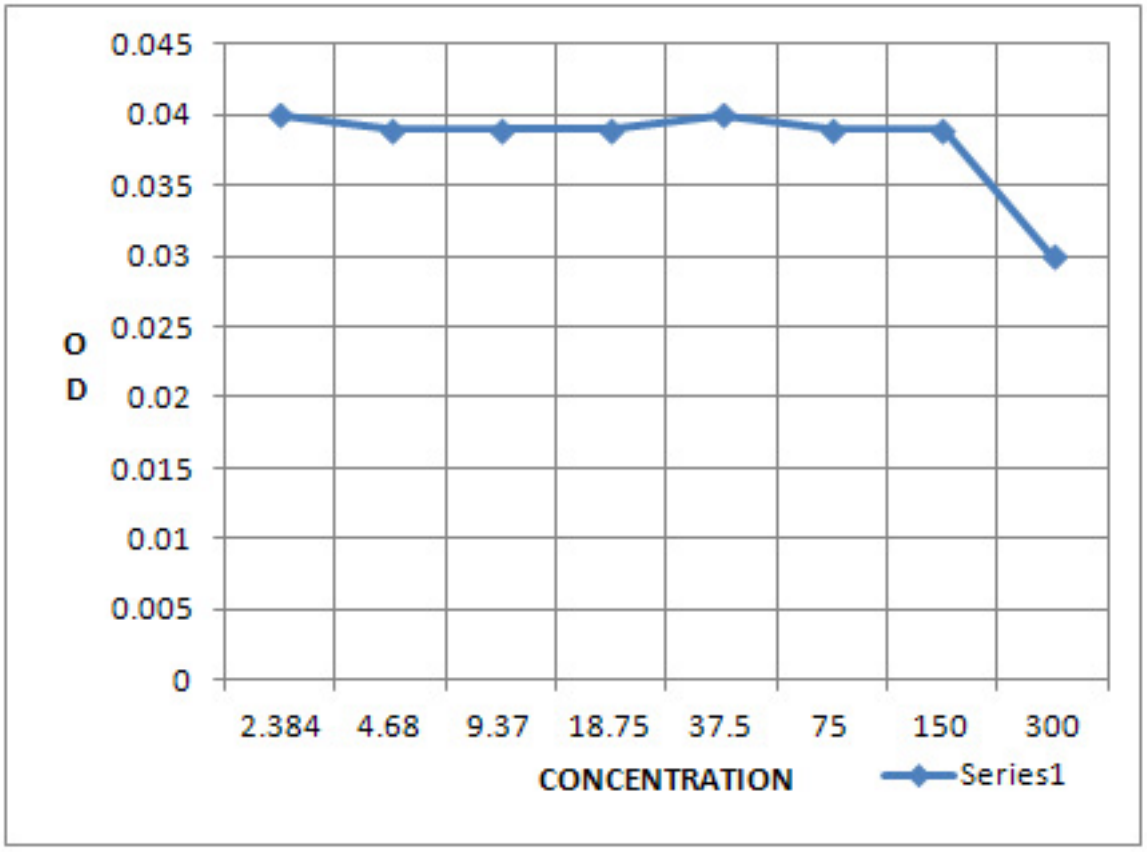
As you see in Diagram 17, antibiotic has shown antimicrobial properties at concentration of 300µg

Diagram 17: comparing light absorbance in different concentrations by (µg) in wavelength of 620nm for Staphylococcus aureus



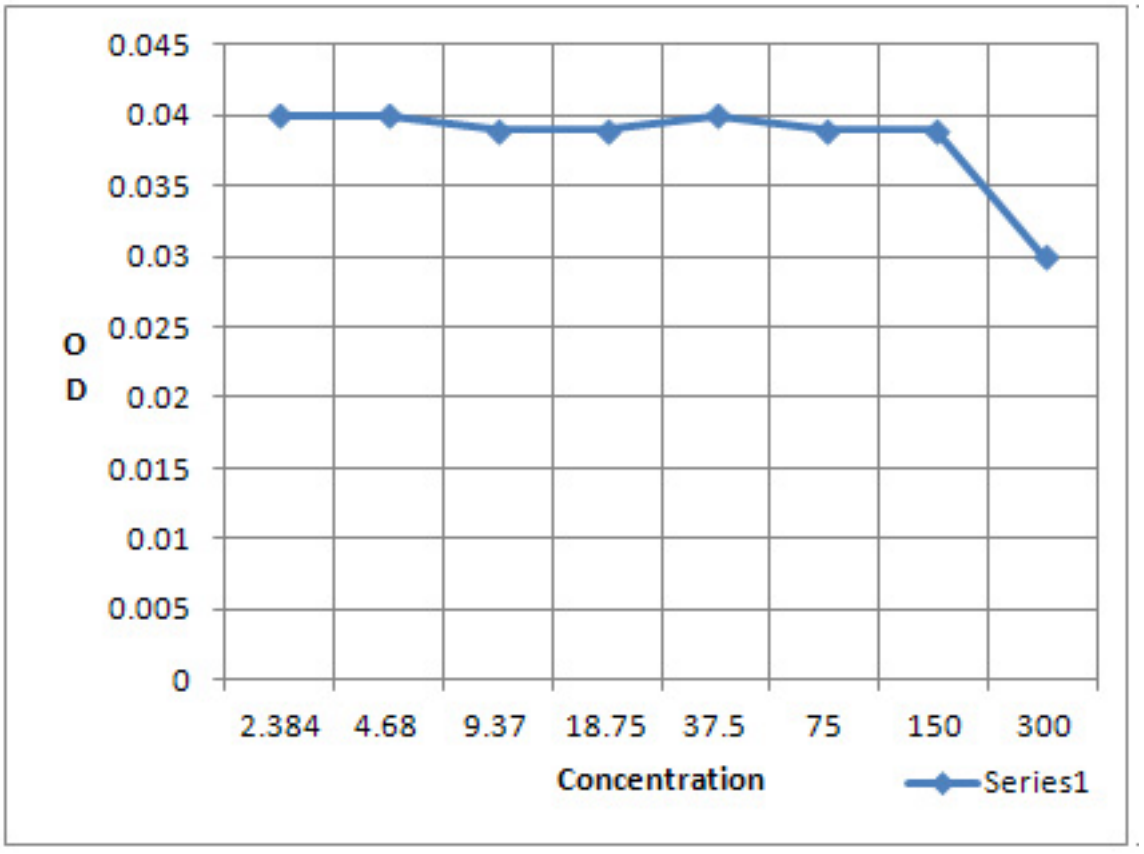
As you see in Diagram 18, antibiotic has shown antimicrobial properties at concentration of 300µg.

Diagram 18: comparing light absorbance in different concentrations by (µg) in wavelength of 620nm for Bacillus subtilis



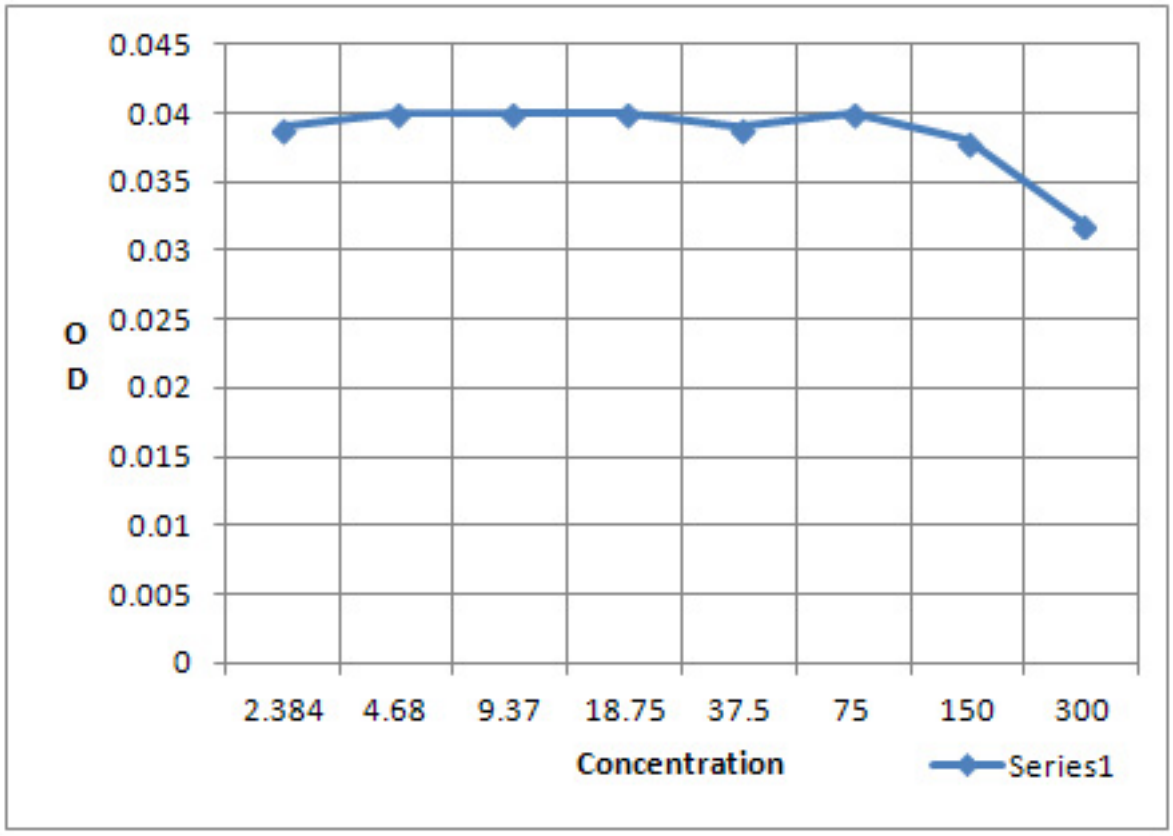
As you see in Diagram 19, antibiotic has shown antimicrobial properties at concentration of 300µg.

Diagram 19: comparing light absorbance in different concentrations by (µg) in wavelength of 620nm for E. coli



As you see in Diagram 20, antibiotic has shown antimicrobial properties at concentration of 300µg.

Diagram 20: comparing light absorbance in different concentrations by (µg) in wavelength of 620nm for Pseudomonas aeruginosa



Discussion

In this study, antimicrobial properties of the derivative peptide of Naja naja snake was examined. The studying peptide sequence includes 13 amino acids, of which their sequence is: DEQSTHGAYVWKL

D: aspartic acid, E: glutamic acid, Q: glutamine, S: serine, T: threonine, H: histidine, G: glycine, A: alanine, Y: tyrosine, V: valine, W: tryptophan, K: lysine, L: leucine, Alanine, valine, and leucine are hydrophobic amino acids in this structure; lysine and histidine have a positive charge and glycine has a role in peptide's flexibility.

Various studies about these peptides' effects have been carried out by researchers as mentioned below:

• Salehi et al. (2012) did a study named D28 peptide's antibacterial effects. Results of this study showed that the D28 peptide has an antimicrobial property against S. aureus.

• Gaiser et al. (2011) studied and examined production of antimicrobial peptides made by bacteria. These peptides showed a good antimicrobial property, due to their pure positive charge and the 3-dimension amphipathic structure.

• Shebl et al. (2012) studied derivative profile of various snakes and examined their antimicrobial and antiviral properties and found their effects relevant to their enzymes' activities. They also concluded that they had a good antimicrobial effect on gram-positives and gram-negatives.

• Samel et al. (2012) carried out a study on effect of derivative A2 phospholipase from some snake species and concluded that it had an antimicrobial effect on gram-positive and gram-negative bacteria.

• Zare et al. (2014) identified a new antimicrobial peptide from amphibians' dermal discharges, which showed its antimicrobial properties against gram-positive and gram-negative bacteria and fungi. Its major effect is against gram-negative bacteria. This peptide was named "Buforin-k".

• Zare et al. (2014) carried out a study on derivative peptide of coriander, which showed a good antimicrobial property against gram-positive (Staphylococcus aureus) and gram-negative (Klebsiella pneumonia) bacteria. It also didn't show hemolytic property against red blood cells. It was concluded that this peptide can be useful to be produced as a drug in treatment of diseases.

• Karbalaie Muhammad et al. (2011) synthesized a peptide that showed good antimicrobial and antineoplastic properties. They concluded that the synthesized peptide applies a good antimicrobial effect on gram-positive and gram-negative bacteria.

The present work examined antimicrobial properties of derivative peptide of cobra (Naja naja) snake's venom and showed that this peptide has antimicrobial effect with sequence of DEQSTHGAYVWKL against gram-positive and gram-negative bacteria, including Staphylococcus aureus, Bacillus subtilis, Escherichia coli and Pseudomonas aeruginosa.

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The Relationship between Personality Characteristics, Locus of Control, and Self-esteem among Nursing Students at Kashan University of Medical Sciences in 2016

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Abstract

This study aimed at investigating the relationship between personality characteristics, locus of control, and self-esteem of nursing and midwifery students of Kashan University of Medical University in 2016. The research method was descriptive and correlational. The population of this study included all nursing and midwifery students of Kashan University of Medical University (N=300) in 2016. 100 subjects were selected as the sample by stratified random sampling and Krejcie Table and 100 questionnaires were analyzed. The data collection tool included three standard questionnaires of Cooper Smith's Self Esteem, Rotter's Locus of Control, and Eysenck's Personality. All three questionnaires were standard and used in many foreign and domestic studies. The reliability of all these questionnaires has been confirmed in many studies indicating a high reliability. In this study, the reliability of the questionnaires was conducted on a 40-subject sample and their statistical estimate through Cronbach's alpha was obtained for extraversion and introversion (r=0.83), emotional stability (r=0.79), lie detectors (r=0.78), locus of control (r=0.76), and self-esteem (r=0.89). The data were analyzed by SPSS software. The results indicated that there is a significant and negative relationship between extraversion and locus of control while 54.9% of the variance of students' internal locus of control can be explained through their extraverted personality. A significant relationship was found between introversion and locus of control as well as between introversion and self-esteem. In addition, there was a positive and significant relationship between extraversion and self-esteem while 47% of the variance of students' self-esteem can be explained through their extraverted personality.

Key words: Personality characteristics, locus of control, self-esteem

Introduction

Human behavior is affected by social factors. Human personality reaches toward perfection when an appropriate balance and interaction is created between human and environment (Tuzandeh Jani, 2007). The question of how personal differences lead to tendency or avoidance in human daily performance has always been answered by the word "personality" (Eliut, 2008). Personality is affected by internal elements such as thoughts, values, and genetic features and external elements such as observable behaviors (Mc Shane & Van Glinow, 2003). Psychologically, the personality characteristics are the basis of behavioral patterns (Nabi Zadeh Chiyaneh, 2010, as cited in Shahandeh and Yousefi, 2011).

One of the important aspects of personality which can be affected by such relationships is the individuals' beliefs in the ability of controlling the consequences of their lives, i.e. the locus of control (MizaeiAlavijeh, et al., 2012). Control can be defined as applying the power, guidance, or avoiding the behavior and actions of others to oneself. Locus of control is an important factor affecting mental health and reducing stress. A human, as a living creature, reacts to the external stimuli which intend to destroy this balance. The reaction of humans to different stimuli is highly dependent on the severity of these stimuli and the effectiveness of each person. Locus of control is the central core of psychological structures in the person providing them with comfort and preventing anxiety (Cleior & Soundler, 1992).

Another component related to personality characteristics is self-esteem. In this regard, Reladov (1984) stated that the higher ability in problem-solving is related to the increase of self-esteem (Salehi & Vakili, 2008). Self-esteem is the emotional dimension evaluating self-concept and equals to the concepts such as self-guard, self-assessment, and self-worth (Hart, 1999, as cited in Beshlideh and Yousefi, 2012).

Preparing the individual's acquisition of knowledge, cognitive skills, and job skills is regarded as one of the most important factors of the educational system. Our society is being developed and self-esteem is one of the most important factors affecting the progress of motivation and academic achievement (Abbasi, 1999). Self-esteem is one of the important factors in human prosperity referring to the personal judgment on self-worth (Vali Zadeh & Emami Pour, 2007). Increasing the academic achievement and the effort for success, having self-confidence, being arrogant and aggressive, showing tendency to better health, enjoying the relationship to others, predicting the later success positively, having close relationships to self–esteem, and being assertive are among the obvious signs of high self-esteem levels in individuals (Ghasemi, 2000). Self-esteem is the most certain internal factors in the mental growth of a person having prominent effects on intellectual flow, feelings, tendencies, values, and goals. As the person fails to acquire self-esteem, he or she may encounter anxiety, mental breakdown, self-pessimism, escaping the truth, and lack of adequacy in life (Mcauly et al., 1997). Self-esteem is regarded as one of the main determinants of thoughts, emotions, feedbacks, and behaviors among individuals . The results showed that self-esteem has different aspects including physical, family, social, and academic self-esteem (Eysenck, 1967; Pop, 1989; Cooper Smitt, 1967).

Studying the students who looked for a job indicated that those with high self-esteem received more job suggestions and were evaluated as more favorable by their employers than those with low self-esteem (Shultez, 2007). Teaching the communication skills affects the promotion of self-esteem, emotional adequacy, and social adequacy among students (Momeni, 2010). Some researchers like Int et al. (1994), Krenter et al. (1991) and Elyas (1991) found teaching life skills as effective on self-esteem, self-concept, and self-efficacy. A negative relationship was found between self-esteem and progress motivation with procrastination. In addition, a positive and significant relationship was observed between self-esteem and progress motivation. Based on the regression, self-esteem has a higher predictability for progress motivation (Avaziyan, et al., 2011). According to California Labor and Workforce Development Agency, responsibility is appreciating the personal significance and value and having a responsible personality and responsible actions in relationship with others (Mahdavi & Enayati, 2010, as cited in Farhadi, 2004). The study results of Clouse and Murgan (2005) showed that the effects of experimental interventions (teaching social skills and the effect of medical treatment) can have the strongest effects on increasing self-esteem (Mahdavi, et al., 2011). Tamanayifar, et al. (2010) stated that the emotional intelligence, self-concept, and self-esteem of students have no effect on their academic achievement. Self-esteem is higher among women, compared to men and there is no difference between emotional intelligence and self-concept, which is one of the fundamental variables of locus of control and self-esteem. Valizadeh and Emami Pour showed that teaching rational treatment-behavioral emotion increases the general, family, and social self-esteem among the students although no effect was reported based on their physical and academic self-esteem (Kelior & Soundler, 1992).

Thus, the present study aimed to investigate the relationship between personality characteristics, locus of control, and self-esteem among nursing and midwifery students in Kashan University of Medical University in 2016 based on the following hypotheses:

H1: There is a relationship between extroversion and locus of control among students.
H2: There is a relationship between introversion and locus of control among students.
H3: There is a relationship between extroversion and self-esteem among students.
H4: There is a relationship between introversion and self-esteem among students.

Methodology

The present study used a descriptive and correlational design. In this study, personality characteristics were considered as predicting variable (independent) and locus of control and self-esteem as criterion variable (dependent). The population of this study included all nursing and midwifery students in Kashan University of Medical Sciences (N=300) in 2016. One hundred subjects were selected based on stratified random sampling and Krejcie Table. In order to collect the related data, 57-item Eysenck's Personality questionnaire, 29-item Rotter's Locus of Control questionnaire and 57-item Cooper Smith's Self Esteem questionnaire were used. All these three questionnaires were standard and have been used in many foreign and domestic studies. In order to measure the reliability of the questionnaires, 40 subjects were selected:

Table 1: The reliability of instruments

Indicator / Variables		N	Cronbach's alpha
Locus of control		40	0.76.
Personality characteristics	Introversion-Extroversion (E)	40	0.83.
	Emotional stability (N)	40	0.79.
	Lie detector (L)	40	0.78.
Self-esteem		40	0.89.

Research findings based on demographic information

Table 2 presents the personality characteristics of the sample. Accordingly, 100 (50 males and 50 females) with the mean age of 22 were selected. Most of the subjects had bachelor's degree (58%).

Table 2: The distribution of the studied sample based on demographic features

Variable		Frequency	Percentage
Gender	Male	50	50
	Female	50	50
Age	20-25 years old	27	27
	26-30 years old	21	21
	31-35 years old	10	10
	36-40 years old	5	5
	41-45 years old	7	7
	45-50 years old	4	4
	Not stated	26	26
Education	Diploma	6	6
	Associate degree	4	4
	Bachelor	58	58
	Master	6	6
	Not stated	26	26
Occupation	Housewife	6	6
	Self-employed	11	11
	Employee	13	13
	Teacher	15	15
	Student	14	14
	Not stated	41	41

Assumption for using parametric statistical test

Based on the results of Kolmogorov-Smirnov test in Table 3, the locus of control (external-internal), personality characteristics and self-esteem have normal distribution since the significance level of all Z values in each variable is larger than 0.05 ($p>0.05$). Therefore, the parametric tests can be used to analyze the research hypotheses.

Table 3: The result of Kolmogorov-Smirnov test for normal distribution of data

Indicator \ Variable		N	Z value	Significance level
Locus of control		100	290.1	072.0
Components	Internal locus of control	21	77.1	053.0
	Locus of control	79	210.1	107.0
Personality characteristics	Introversion-Extroversion	100	777.0	582.0
	(Emotional stability N)	100	210.1	107.0
	Lie detector (L)	100	341.1	055.0
Self-esteem		100	093.1	183.0

Research hypothesis testing

H1: There is a relationship between extroversion and locus of control among the students.

Based on the results of Pearson correlation test in Table 4, there is a negative and significant relationship between extroverted personality and locus of control (p = 0.000 and r = -0.737). Therefore, higher extroverted personality leads to more internal locus of control and vice versa.

H2: There is a relationship between introversion and locus of control among the students.

Based on the results obtained from Pearson correlation test, there is no significant relationship between introverted personality and locus of control (p = 0.998, r = -0.003).

Table 4: The relationship between personality characteristic and locus of control among students

Variables	N	Correlation coefficient	Sig.
The relationship between extroverted personality and locus of control among students	71	-737.0	**000.0
The relationship between introverted personality and locus of control among students	29	-003.0	989.0

* Significant at 0.05 level ** significant at 0.01 level

H3: There is a relationship between extroversion and self-esteem among the students.

Based on the results of Pearson correlation test in Table 5, there is a positive and significant relationship between extroverted personality and self-esteem (p = 0.000 and r = 0.686). Therefore, with a confidence of 99%, the higher extroverted personality, leads to more self-esteem and vice versa.

H4: There is a relationship between introversion and self-esteem among the students.

Based on the results of Pearson correlation test, no significant relationship was observed between introverted personality and self-esteem (p = 0.65; r = 0.347).

Table 5: The relationship between personality characteristic and self-esteem among the students

Variables	N	Correlation coefficient	Sig.
The relationship between extroverted personality and self-esteem in students	71	686.0	**000.0
The relationship between introverted personality and self-esteem in students	26	347.0	065.0

* Significant at 0.05 level ** significant at 0.01 level

Discussion and Conclusion

The results based on the first hypothesis suggested that the personality characteristics of extroversion have a negative and significant relationship with locus of control. The findings of this research are consistent with the studies of Ghasemi (2001), Holmes (2000) and Jashni (2014) indicating a negative and significant relationship between extroverted personality and locus of control. However, the results of this study are inconsistent with the study of Ghasemi (1384) showing no relationship between the extroverted personality and locus of control. Regarding the second hypothesis, the personality characteristics of introversion has no relationship with locus of control. The findings are incongruent with the studies of Vafai (2001), Holmes (2000), and Ghasemi (2001), in which they reported the significant relationship between introverted personality and locus of control. However, the results are congruent with the study of Jashni et al.(2014).

Regarding the third hypothesis, the personality characteristics of extroversion has a positive and significant relationship with self-esteem. The findings are in line with the studies of Schultz (2001), Biabangard(2003), Nanel (2005), Sidney Allen (1930), Tatiana (1997), Gary Mazet (1960), and Jashni et al.(2014).

As for the fourth hypothesis, upon which the personality characteristics of introversion have no relationship with self-esteem, the findings are in line with the studies of Schultz (2001), Biabangard (2003), Nanel (2005), Sidney Allen (1930), Tatiana (1997), Gary Mazat (1960), but inconsistent with the study of Jashni et al. (2014).

Limitations of the study

Based on the results of the present study, the following limitation should be considered:

1. Limiting the statistical population of the study to the students in Kashan University of Medical Sciences
2. Limiting the data collection tool to the questionnaire and not using other methods of data collection such as interview, observation, etc.
3. The cultural weakness of the study and the reluctance of some students in answering the questions
4. Some respondents may have not expressed their true feelings and emotions, and personal anxiety may have affected their responses.
5. Some uncontrolled variables such as field of study, personality type, and cultural characteristics of individuals may have influences the results of the study.

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