ASIAN JOURNAL OF BIOMEDICAL & PHARMACEUTICAL SCIENCES

e-ISSN: 2249-622X

RESEARCH ARTICLE

Vitamin B_{12} and Folate Status in Sudanese Psychiatric Patients

Ezeldine K. Alturabi[1], Ahmed K. Bolad[2]*, AbdelRahman Tambal[3], Ahmed Hamad[4], Modasir Ali[5], Elhassan Eltom[6], Mohamed Kheshin[5], Mohamed F. Lutfi[7]

[1] Department of Pathology, Faculty of Applied Medical Science, Northern Border University, KSA

[2]* Department of Microbiology, Faculty of Medicine, University of Al-Neelain, Sudan

[3] Department of Pathology, Faculty of Medicine, The National Ribat University, Sudan

[4] Department of Medicine, Faculty of Medicine, Northern Border University, KSA

[5] Faculty of Medical Laboratory Science, University of Al-Neelain, Sudan

[6] Department of Pharmacology, Faculty of Applied Medical Science, Northern Border University, KSA

[7] Department of Physiology, Faculty of Medicine, University of Al-Neelain; Sudan

Received:
22nd April 2013
Received in revised form:
29h April 2013
Accepted:
4th May 2013
Available online:
5th May 2013

Online ISSN 2249–622X
http://www.jbiopharm.com

ABSTRACT

Background: The contribution of B_{12} and folate deficiencies to pathophysiology of psychiatric illnesses is well known worldwide, however it was not evaluated in Sudanese psychiatric patients.

Aim: To assess the association between the neuropsychiatric syndromes and the levels of both vitamin B_{12} and folic acid in Sudanese psychiatric patients.

Materials and Methods: The study involved a test group of 100 psychiatric patients and an age/gender matched control group of 100 subjects with no past history of psychiatric illness. Laboratory investigations, including complete blood count (CBC), serum vitamin B_{12} and folate concentrations were done to all studied subjects. Significance of the difference in the means of the studied variables and the association between psychiatric illnesses and both B_{12} or folic acid deficiencies were assessed using appropriate statistical tests.

Results: Most of hematological indices were significantly less in psychiatric patients, although their means were within normal range. The serum concentrations of vitamin B_{12} in the psychiatric patients (M±SD = 527.9 ± 305. 8 pg/ml) were significantly lower compared with the control group (M±SD = 590.5± 186.1 pg/ml, P = 0.001). There was significant association between B_{12} deficiency and psychiatric illnesses (P = 0.014). Six percent of the psychiatric patients were suffering from B_{12} deficiency while none the control group was suffering from the same deficiency. The serum concentrations of folic acid were comparable in both studied groups (M±SD = 7.2 ± 1.7 ng/ml, 7.2 ± 2.6 ng/ml in the control and test groups respectively, $P > 0.05$). There was no folic acid deficiency in both test and control groups.

Conclusion: There was association between vitamin B_{12}, but not folic acid, deficiency and psychiatric diseases in studied Sudanese subjects. Most of the hematological indices were significantly less in psychiatric patients, although their means were within normal range. The significantly lower levels of vitamin B_{12} deficiency were not associated with megaloblastic changes.

Key words: folic acid, megaloblastic, psychiatric, vitamin B_{12}, Sudanese.

1. INTRODUCTION

Vitamin B_{12} and folate are essential for proper central methionine/homocysteine metabolism [3, 4] and hence nervous system function [1, 2]. Both vitamins are involved in synthesis of nucleic acids and certain

*Corresponding author: Ahmed K. Bolad, Department of Microbiology, Faculty of Medicine, University of Al-Neelain, Sudan| Email: aaabolad@hotmail.com

neurotransmitters [5-9]. An important consequence of the deficiency of these vitamins is hyperhomocysteinemia, which causes several neuropsychiatric disorders [10, 11], and megaloblastic anemia. Interestingly, there is a significant inverse relationship between the degree of B_{12} deficiency anemia and the severity of neurological manifestations. Patients without anaemia or macrocytosis tend to have the most severe nervous system involvement [12, 13]. The neuropsychiatric effects of folate deficiency are remarkably similar to vitamin B_{12} deficiency. Neuropsychological studies attributed schizophrenia [14], impairments of intellectual function including attention and abstract reasoning to folate deficiency [1]. Up to one third of psychiatric admissions have low serum folate concentrations, mostly without anaemia or macrocytosis [15].

In Sudan, there are no previous studies evaluating these two vitamins in Sudanese psychiatric patients. The contribution of B_{12} and folate deficiencies to pathophysiology of psychiatric illnesses in Sudan is still uncertain. This study aimed to assess the association between the neuropsychiatric syndromes in Sudanese psychiatric patients and the levels of both vitamin B_{12} and folic acid.

2. MATERIALS AND METHODS

The study was conducted during the period December 2009 - November 2011 in the three major psychiatric hospitals in Khartoum state – Sudan, namely, Altigani Almahi psychiatric hospital, Taha Bashr psychiatric hospital and the psychiatry unit of Khartoum teaching hospital. The ethical approvals were received from the institutional review board of the hospitals of concern.

The study involved two groups: a test group of one hundred psychiatric patients selected randomly from above-mentioned hospitals and age/gender matched control group of one hundred subjects with no past history of psychiatric illness. The medical history and clinical status of the patients were assessed by well trained psychiatric physician. Laboratory investigations, including complete blood count (CBC), serum vitamin B12 and serum folate were performed to all studied subjects. The CBC was measured using Sysmex KX-21N-TOA - Medical Electronics Company - Japan. Serum vitamin B12 and serum folate levels were measured using the Electrochemiluminescence (ECL) technology (ELECSYS 2010 - Rhoche diagnostic- Germany). Based on the kit manufacturer (Rhoche diagnostic- Germany), the normal range for cobalamin was 197–866 pg/ml in both males and females. Regarding folic acid, the normal ranges were 2–15 ng/ml in the males and 2–9.1 ng/ml in in the females.

Statistical evaluation was performed using the Microsoft Office Excel (Microsoft Office Excel for windows; 2007), SPSS (SPSS for windows version 19) and OpenEpi version 2.3.1. Normal distribution of studied variables was examined using Kolmogorov-Smirnova and Shapiro-Wilk tests. Unpaired T-test and Mann-Whitney U test were used to assess significant difference in the means of the studied variables in the different groups. The association between either B_{12} or folic acid deficiencies and psychiatric illnesses were assessed using fisher extract test. $P < 0.05$ was considered significant.

3. RESULTS

As shown in figure 1, the control group is well matched for age ($P = 0.794$) and gender ($P = 0.565$) with the test group. Most of the hematological indices were significantly higher in the control group compared to patients with psychiatric illnesses (table 1). In contrast, mean corpuscular volume (MCV) and the white cells other than neutrophils and lymphocytes (Mix %) were not significantly different in the studied groups.

The serum concentration of vitamin B_{12} in the psychiatric patients (M±SD = 527.9 ± 305. 8 pg/ml) was significantly lower compared to the control group (M±SD = 590.5± 186.1 pg/ml, $P = 0.001$) (figure 1). There was significant association between B_{12} deficiency and psychiatric illnesses ($P = 0.014$) (table 2). Six percent of the psychiatric patients were suffering from B_{12} deficiency while none the control group was suffering from the same deficiency. Alternatively, the serum concentration of folic acid was comparable in both studied groups (M±SD = 7.2 ± 1.7 ng/ml, 7.2 ± 2.6 ng/ml in the control and test group respectively, $P > 0.05$) (Figure 3). There was no folic acid deficiency in both test and control groups.

	Control Group (N = 100) M ± SD	Psychiatric patients (N = 100) M ± SD	*P-value*
WBC ($\times 10^3/\mu l$)	5.5 ± 1.6	5.1 ± 1.9	0.017*
RBC ($\times 10^6/\mu l$)	5.0 ± 0.4	4.8 ±0.4	0.006*
Hb (g/dl)	14.1 ± 1.4	13.2 ± 1.7	0.000*
Hct (%)	42.2 ± 3.9	40.5 ± 4.4	0.012*
MCV (fl)	83.5 ± 4.3	83.5 ± 5.5	0.712
MCH (pg)	28.0 ±1.8	27.0 ± 2.3	0.001*
MCHC (g/dl)	33.4 ± 1. 6	32.7 ± 1.6	0.007*
PLT ($\times 10^9$/l)	238 ± 69	209 ± 92.7	0.021*
Lymphocytes (%)	37.6 ± 7.5	42.3 ± 10.2	0.000*
Neutrophils (%)	52.9 ± 8.3	48.8 ± 10.0	0.002*
Mix (%)	9.7 ± 2.8	9.0 ± 3.2	0.093

Table 1: The hematological findings in studied groups

A. B_{12} Deficiency * Psychiatric Illness cross-tabulation

		Psychiatric Illness		Total
		(+)	(-)	
B_{12} Deficiency	(+)	6 (3%)	0 (0%)	6 (3%)
	(-)	94 (47%)	100 (50%)	194 (97%)
Total		100 (50%)	100 (50%)	200 (100%)

P (Fisher extract) = 0.014

B. Risk-based estimates

Point Estimates	Value	95% Confidence Intervals
Risk in patients with B_{12} deficiency	100%	55.72 - 100
Risk in patients without B_{12} deficiency	48.45%	41.52 - 55.45
Overall Risk	50%	43.14 - 56.86
Risk Ratio	2.064	1.785 - 2.386
Risk Difference	51.55%	44.51 - 58.58
Etiologic fraction in population	3.093%	0.5848 - 5.601
Etiologic fraction in patients with B_{12} deficiency	51.55%	43.98 - 58.09

Table 2: The association between B_{12} deficiency and psychiatric illness

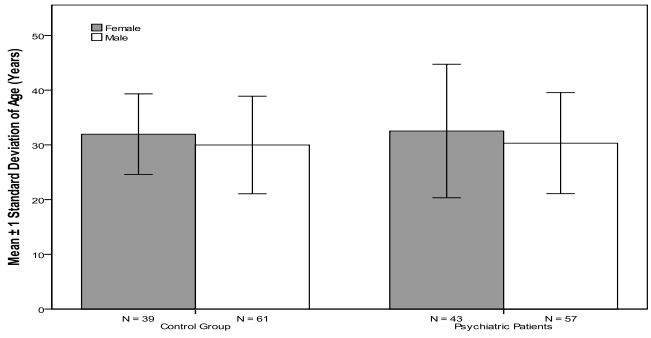

Figure 1: Distribution of age and gender among studied groups.

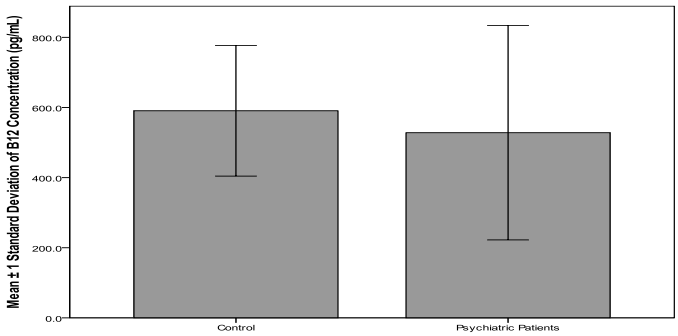

Figure 2: Concentration of vitamin B_{12} in studied groups.

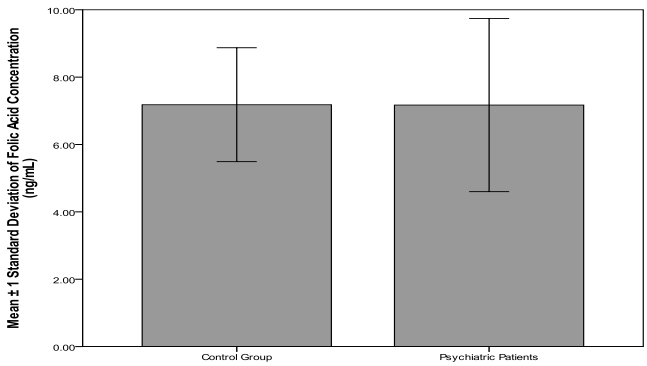

Figure 2: Concentration of folic acid in studied groups

4. DISCUSSION

The current results have added further evidence for the association between vitamin B_{12} deficiency and neuropsychiatric disorders [16-21]; though it is the first study that confirms this fact is Sudanese. The observed association between B_{12} deficiency and psychiatric disorders was a reproducible finding in a variety of psychiatric illnesses including delirium, hallucinations depression, dementia and catatonia [22, 23].

Internationally, the prevalence of vitamin B_{12} deficiency in those suffering from neuropsychiatric disorders is uncertain [24]. In the present study 6% of psychiatric patients were suffering from below vitamin B_{12} deficiency while none of them was suffering from folic acid deficiency. The prevalence of vitamin B_{12} and folic acid deficiencies were relatively higher in elder Israeli subjects accounting for 12.6% and 16.4% respectively [20]. The high prevalence of vitamin B_{12} and folic acid deficiencies among Israeli psychiatric patients were attributed to genetic and environmental factors. Other studies demonstrated vitamin B_{12} deficiency in chronically ill psychotic patients with adequate nutrition thus excluding abnormal eating habits or dietary deficiencies as causative factor [25]. The underplaying etiology of vitamin B_{12} and folic acid deficiencies among psychiatric patients seems to be mysterious and needs to be investigated more. Regarding folate level in psychiatric patients, previous reports showed mixed findings. Folate deficiency was demonstrated in elderly with declined cognitive function [26], patients with depression, dementia, schizophrenia [27] and other psychiatric disorders [28]. Interestingly, Skerritt reported that, although there is a trend for psychiatric patients to have lower serum folate levels than controls, there is no statistically significant difference in folate levels as measured by red cell folate [29]. Other studies failed to demonstrate significant difference in folic acid concentrations between patients with different psychiatric disorders and healthy controls [30, 31]. In the current study the levels of serum folate in the patients and the control groups were comparable adding more evidence for the

variations in folic acid concentrations among psychiatric patients.

Complete blood counts were within normal range in the control group as well as in psychiatric patients. However, the psychiatric patients showed slightly lower white cell and platelets counts which could be attributed to their significantly lower levels of B_{12} [32]. In contrast, there was no evidence of megaloblastic changes in psychiatric patients as indicated by the comparable mean corpuscular volumes of psychiatric patients and the control group. The examination of peripheral blood smears showed no macrocytosis; neither in psychiatric patients nor in control group. Although the mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration were slightly more in the control group compared to psychiatric patients, the difference in the mean reached statistical significance. These findings are consistent with some previous studies [17, 18] but not others [12, 33]. Vladimir *et al* data demonstrated significantly lower levels of vitamin B_{12} and folate, yet there was no evidence of anemia or (mean hemoglobin concentration and mean corpuscular volume were 14.1 g/dl and 90.3 fl respectively) macrocytosis [17]. The findings of Vladimir *et al* was further supported by the results of Engelborghs and his colleges [18]. 20% of the patients by Engelborghs were suffering from vitamin-B_{12} deficiency and 25% of them were having folate responsive neuropsychiatric syndromes; however, there were no evidences of megaloblastic anaemia in both groups [18]. Absence of features of anemia and macrocytosis is difficult to explain, but theoretical speaking may indicate that psychiatric manifestations could appear at early stages of vitamin B_{12} and/or folate deficiency compared to megaloblastic anemia. This hypothesis is partially supported by Berlinsky *et al* who showed relatively low sensitivities of high MCV level as a diagnostic for folic acid and vitamin B_{12} deficiencies (sensitivity were 42.9%, 23.1% for folic acid and vitamin B_{12} deficiencies respectively) [33].

To date there is no universal agreement for the normal range of serum cobalamin levels. However, the high incidence of hematologic, neurologic and gastrointestinal abnormalities in patients with serum cobalamin levels below 300 pg/ml guide the researchers in this field to suggest 300-350 pg/ml as a lower limit for serum cobalamin [34]. Alternatively, maximum mental functions may be reached at a concentration of 1000 pg/ml [35]. In the current study, the mean of serum concentration of vitamin B_{12} in the psychiatric patients (527.9 pg/ml) was not that far away the control group (590.5 pg/ml); however, there were much variations in the vitamin B_{12} concentrations in the former group (standard deviations were 305. 8 and 186.1 pg/ml in the test and the control groups respectively). Statistically, this suggest that the lower values of serum concentration of vitamin B_{12} in psychiatric patients were around 200 pg/ml which could be the range were mental manifestations dominate over hematological finding. However, further studies are desirable to clarify this hypothesis.

In conclusion, the present study provided additional prove for the considerable association between vitamin B_{12}, but not folic acid, deficiency and psychiatric diseases. In addition, most of the hematological indices were significantly less in psychiatric patients, although their means were within normal range. Interestingly, and as reported by other studies [12, 13], the significantly lower levels of vitamin B_{12} deficiency was not associated with megaloblastic changes.

5. ACKNOWLEDGEMENT

The authors would like to thank every contributor for their valuable comments, hosting this work and to those who made this work possible. We also wish to thank Abdel Moneim Salih and Dr. Ramaze Elhakim for their help and support.

6. REFERENCES

1. Reynolds EH. Benefits and risks of folic acid to the nervous system. J Neurol Neurosurg Psychiatry. 2002; 72: 767–771.
2. Quadri P, Fragiacomo C, Pezzati R, Zanda E, Tettamanti M, Lucca U. Homocysteine and B-vitamins in mild cognitive impairment and dementia. Clin Chem Lab Med. 2005; 43: 1096–2000.
3. Carmel R. Megaloblastic anemias: Disorders of impaired DNA synthesis. In: Greer JP, Foerster J, Lukens JN, Rodgers GM, Paraskevas F, Glader B (eds). Wintrobe's clinical hematology. 11th ed. Philadelphia:Lippincott Williams and Wilkins;2004:1367–1395.
4. Smythies JR, Gottfries CG, Regland B. Disturbances of one-carbon metabolism in neuropsychiatric disorders: a review. Biol Psychiatry. 1997;41:230-233.
5. Chiang PK, Gordon RK, Tal J et al. S-adenosylmethionine and methylation. FASEB J.1996; 10:471–480.
6. Bottiglieri T, Hyland K, Reynolds EH. The clinical potential of ademethionine (S-adenosylmethionine) in neurological disorders. Drugs 1994; 48: 1137–1152.
7. Smulders YM, Smith DE, Kok RM et al.Cellular folate vitamer distribution during and after correction of vitamin B12 deficiency: a case for the methylfolate trap. Br. J. Haematol. 2006;132: 623–629.
8. Finkelstein JD. Pathways and regulation of homocysteine metabolism in mammals. Semin. Thromb. Hemost. 2000;26:219–225.
9. Smith, T. P., Cruz, C. P., Brown, A. T., Eidt, J. F. & Moursi, M. M. Folate supplementation inhibits intimal hyperplasia induced by a high-homocysteine diet in a rat carotid endarterectomy model. J. Vasc. Surg.2001; 34: 474–481.
10. Yoo, J. H., Chung, C. S. & Kang, S. S. Relation of plasma homocysteine to cerebral infarction and cerebral atherosclerosis. Stroke.1998; 29: 2478–2483.
11. Kruman, I. I., Kumaravel, T. S., Lohaani, A., Pedersen, W. A., Cutler, R. G., Kruman, Y., Haughey, N., Lee, J., Evans, M. & Mattson, M. P. Folic acid deficiency and homocysteine impair DNA repair in hippocampal neurons and sensitize them to amyloid toxicity in experimental models of Alzheimer's disease. J. Neurosci. 2002;22: 1752–1762.
12. Sethi NK, Robilotti E, Sadan Y . Neurological Manifestations Of Vitamin B-12 Deficiency. The Internet Journal of Nutrition and Wellness.2005; 2. 198-201.

13. Healton EB, Savage DG, Brust JC, Garrett TJ, Lindenbaum J. Neurologic aspects of cobalamin deficiency. Baltimore: Medicine; 1991;70:229-245.
14. Koury MJ, Ponka P. New insights into erythropoiesis: the roles of folate, vitamin B12, and iron. *Annu Rev Nutr* 2004; 24: 105–131.
15. García-Miss Mdel, R; Pérez-Mutul, J; López-Canul, B; Solís-Rodríguez, F; Puga-Machado, L; Oxté-Cabrera, A; Gurubel-Maldonado, J; Arankowsky-Sandoval, G. Folate, homocysteine, interleukin-6, and tumor necrosis factor alfa levels, but not the methylenetetrahydrofolate reductase C677T polymorphism, are risk factors for schizophrenia. *Journal of psychiatric research* 2010;44: 441–446.
16. Yener Güzelcan and Peter van Loon. Vitamin B12 status in patients of Turkish and Dutch descent with depression: a comparative cross-sectional study. Annals of General Psychiatry. 2009;8:18.
17. Vladimir L, Michael K,Tzvi D,Tsvi R, Ram K, Chanoch M. Vitamin B12 and folate serum levels in newly admitted psychiatric patients. Clinical Nutrition. 2006 ;25: 60–67.
18. Engelborghs S, Vloeberghs E, Maertens K, et al. Correlations between cognitive, behavioural and psychological findings and levels of vitamin B12 and folate in patients with dementia. Int J Geriatr Psychiatry 2004; 19: 365–370.
19. Clarke R, Grimley Evans J, Schneede J, et al. Vitamin B12 and folate deficiency in later life. Age Ageing 2004; 33: 34–41.
20. Figlin E, Chetrit A, Shahar A, et al. High prevalences of vitamin B12 and folic acid deficiency in elderly subjects in Israel. Br J Haematol 2003;123:696–701.
21. Carmel R, Vasireddy H, Aurangzeb I, et al. High serum cobalamin levels in the clinical setting: clinical associations and holo-transcobalamin changes. Clin Lab Haematol 2001;23:365–371.
22. Hector M, Burton JR. What are the psychiatric manifestations of vitamin B12 deficiency? J Am Geriatr Soc. 1988;36:1105–12.
23. Berry N, Sagar R, Trpathy BM. Catatonia and other psychiatric manifestation of vitamin B12 deficiency and related issues. Acta Psychiatr Scand. 2003;108:156–9.
24. Oh R, Brown DL. Vitamin B12 deficiency. Am Fam Physician. 2003 Mar 1;67(5):979-86.
25. Silver H. Vitamin B12 levels are low in hospitalized psychiatric patients. Isr J Psychiatry Relat Sci. 2000;37(1):41-5.
26. Fioravanti M, Ferrario E, Massaia M, Cappa G, Rivolta G, Grossi E, Buckley AE. Low folate levels in the cognitive decline of elderly patients and the efficacy of folate as a treatment for improving memory deficits. Arch Gerontol Geriatr. 1998 Jan-Feb;26(1):1-13.
27. Young SN, Ghadirian AM. Folic acid and psychopathology. Prog Neuropsychopharmacol Biol Psychiatry. 1989;13(6):841-63.
28. Lerner V, Kanevsky M, Dwolatzky T, Rouach T, Kamin R, Miodownik C. Vitamin B12 and folate serum levels in newly admitted psychiatric patients. Clin Nutr. 2006 Feb;25(1):60-7.
29. Skerritt UM. A prevalence study of folate deficiency in a psychiatric in-patient population. Acta Psychiatr Scand. 1998 Mar;97(3):228-32.
30. Penninx BWJH, Guralnik JM, Ferrucci L, Fried LP, Allen RH, Stabler SP: Vitamin B12 deficiency and depression in physically disabled older women: epidemiologic evidence from the Women's Health and Aging Study. Am J Psychiatry 2000; 157:715–721.
31. Reif A, Pfuhlmann B, Lesch KP. Homocysteinemia as well as methylenetetrahydrofolate reductase polymorphism are associated with affective psychoses. Prog Neuropsychopharmacol Biol Psychiatry 2005; 29: 1162-1168.
32. Van Dyck CH, Lyness JM, Rohrbaugh RM, Siegal AP. Cognitive and psychiatric effects of vitamin B12 replacement in dementia with low serum B12 levels: a nursing home study. Int Psychogeriatr. 2009 Feb;21(1):138-47.
33. Berlinsky S, Serov B, Shiber A. Erythrocyte mean corpuscular volume of psychiatric patients Harefuah. 1993 Sep;125(5-6):138-41, 192, 191.
34. Chanarin I, Metz J. Diagnosis of cobalamin deficiency: the old and the new. Br J Haematol 1997;97:695–700.
35. Dommisse J. Subtle vitamin-B12 deficiency and psychiatry: a largely unnoticed but devastating relationship? Med Hypotheses.1991;34:131–140.

Conflict of Interest: None Declared

Cite this article as:
Ezeldine K. Alturabi, Ahmed K. Bolad, AbdelRahman Tambal, Ahmed Hamad, Modasir Ali, Elhassan Eltom, Mohamed Kheshin, Mohamed F. Lutfi. Vitamin B_{12} and Folate Status in Sudanese Psychiatric Patients. Asian Journal of Biomedical and Pharmaceutical Sciences, 2013, 3: (19), 22-26.

