



OUTLOOK
2016

4

NAHLAA A. KHALIFA
AND ELHAM A. ALJAALY*

The Involvement of nutraceuticals to sustainable healthcare in Europe in the context of Major Depressive Disorder (MDD)

Clinical Nutrition Department,
Faculty of Applied Medical Sciences,
King Abdulaziz University,
P.O. Box: 54539, Jeddah 21524, Saudi Arabia
E-mail: nahlaakhalifa@outlook.com
E-mail: nkhalefa@kau.edu.sa
E-mail: ealjaaly@kau.edu.sa
E-mail: aljaalydiet@gmail.com

ABSTRACT

Purpose: Study evidence-based records on some effective nutraceuticals to be involve in Europe in Major Depression Disorder (MDD) management. Represent nutraceuticals anti-depressant properties to achieve the European health policy targets 'Investing in Health' and upkeep sustainable healthcare systems.

Methodology: Gaining literature by searching MEDLINE (PubMed), Google Scholar, PsychINFO and Quartile databases and retrieving relevant published articles in the peer-reviewed journals.

Findings: Results provided evidence of a range of nutraceuticals, which are of potential benefits in management of depression. Studies support the anti-depressant properties of S-Adenosyl Methionine (SAME), Folic acid, 5-hydroxytryptophan (5-HTP) and omega-3 fatty acids. The results might give evidence for innovative adjunctive neurobiological line for managing and treating depression in Europe.

*Corresponding author





**N.A. Khalifa
and E.A. Aljaaly**

Practical implications: Randomised controlled trials and evaluation process continue to provide evidence for the nutraceuticals use for depression.

Social implications: Nutraceuticals emphasise the Person-focused Medicine, which offers a psychophysical balance to the individual.

Originality/value: Nutraceuticals have specific antidepressant properties that found to be of benefit in psychiatric population and reduce the pharmacotherapeutic side effects.

Keywords: Complementary and Alternative Medicine; CAM; nutraceuticals; depression; anti-depressant; S-Adenosyl Methionine; SAME; folic acid; 5-hydroxytryptophan; 5-HTP; Omega-3; sustainability; Europe.

INTRODUCTION AND OBJECTIVES

An overview of the problem

European public health is under intensifying challenges from a different social, political, environmental and lifestyle factors. Depression shows a large challenge for public health affecting on economic activity, social life, learning and value of life beyond than most physical diseases, and in particular reported cases can lead to suicide attempts or suicide. According to the first report from the European Outcome of Depression International Network (ODIN) study done by Ayuso-Mateos et al. (2001), depressive disorder is an extremely prevalent condition in Europe as it is reported to be 8.5% of which female average around 10% and male at 6.6% with great occurrence (urban UK and urban Ireland), little occurrence (urban Spain) and average occurrence (the remaining places). According to study done by Curran et al. (2007), on mental health and employment, depression exemplifies the main reason of absence from work and premature retirement in many European countries. Additionally Sobocki et al. (2006) reported that depression is considered as the most expensive brain disorder in the region, accounting for 33% of their total cost. The World Health Organization (2013) reported that among the 20 countries with the maximum suicide percentages in the world, six are in the European region and annually there is about 1 out of 15 people affected by depression in the WHO European region and 4 out of 15 suffer if anxiety and all forms of depression are involved (Figure 1).





Figure 1 Depression in the WHO European Region, www.euro.who.int/mental health

The involvement of nutraceuticals to sustainable healthcare in Europe in the context of MDD

Although the advancement of the psychopharmacological during the past few years, and the better effects than several years ago, however major depression controlling still a challenge faced mental health workers. Patients, who are not satisfied with conventional treatment, look for other way of treatments especially Complementary and Alternative Medicine (CAM) either in combination with conventional treatment or alone. According to Herman et al. (2012), CAM is cost-effective, safe and well tolerated by patients with mental and physical conditions.

MAJOR DEPRESSION DISORDER (MDD)

Is a psychological condition described by a general and determined low mood that is accompanied by loss of pleasure or interest in usually pleasant activities and loss of self-esteem.(Salmans, 1997).

THE PATHOPHYSIOLOGY OF MDD

The main physiological changes that involve in MDD are neuro-endocrinological alterations, decrease in brain-derived neurotrophic factor, cytokine changes and monoamine impairment (Belmaker and Agam, 2008). There is the possibility to provide a more broad therapeutic biological method to treat depression through pointing an array of these main neurobiological pathways by specific nutraceuticals (Omega-3 fatty acids, S-adenosyl methionine (SAME), Folinic acid and 5-hydroxytryptophan (5-HTP).





**N.A. Khalifa
and E.A. Aljaaly**

NUTRACEUTICALS

According to Kalra (2003), nutraceutical defined as a wide word which is utilised in describing some substance resulting from food origin with more health profits as well as the essential nutritional worth of foods. It chains two verses 'nutrient' (a nutritious food constituent) plus 'pharmaceutical' (A Medical Remedy) which were joined in 1989 by the creator and chairman of the Foundation of Innovation Medicine, Stephen L. DeFelice. Nutraceutical is applied to products that range from herbal products, dietary supplements, isolated nutrients, and specific diets and processed foods such as soups, beverages and cereals, that supposedly offers health or medicinal benefits, involving the treatment and prevention of disease. The Nutraceutical role in human nutrition is one of the most significant areas of study, with wide implications for healthcare providers, consumers, food distributors and producers.

S-ADENOSYL METHIONINE

SAMe is a molecule found in body fluids and tissues. It is formed from adenosine triphosphate and L- methionine (Bottiglieri et al., 1988). SAMe was initially determined in Italy by Cantoni (1952). It was discovered to be an effective cofactor in biological methylation reactions by Cantoni as a physiological giver of methyl groups to a variety of molecules in body (Kresge et al., 2005). Moreover, it is converted into homocysteine and adenosine (Baldessarini, 1987). Figure 2 it is involved in several cellular functions including the metabolism and synthesis of neurotransmitters (Gören et al., 2004). SAMe might also improve depression through augmented serotonin turnover, decreased prolactin secretion, reuptake inhibition of norepinephrine, enhanced dopaminergic action, and increased phosphatidylcholine conversion (Papakostas, 2009). Although SAMe has been sold in particular European countries for many years for depression and other medical conditions (Shippy et al., 2004) But, it is not approved legally for the treatment of depression in the United Kingdom (UK).

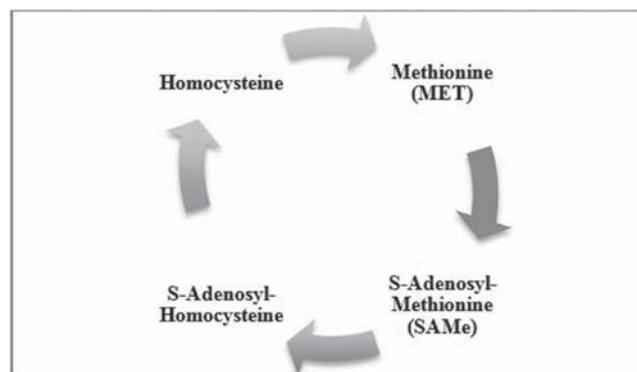


Figure 2 Conversion of methionine to Homocysteine (Methyle transfer reaction)
Source: Khalifa (2016, unpublished work).





L-FOLINIC ACID (THE ACTIVE FORM OF FOLATE)

Some studies in the literature propose that depression is related to folate deficiency (Coppen and Bolander-Gouaille, 2005). Additionally patients who has folate deficiency either have a slighter improvement, a more severe depressive incident, or greater probabilities of relapse when taking antidepressants (Fava, 1997). A positive result was found when using folic acid with anti-depressant in improving the antidepressant response rates (Coppen and Bailey, 2000). Folate was found to be involved in the formation and metabolism of various monoamines especially with the formation of SAMe from homocysteine (Fava and Mischoulon, 2009).

The involvement of nutraceuticals to sustainable healthcare in Europe in the context of MDD

5-HYDROXYTRYPTOPHAN (5-HTP)

5-HTP, which is resulting from L-tryptophan is an important monoamine precursor that is needed for the formation of serotonin (Byerley et al., 1987). A study done by Shaw et al. (2002) on 5-HTP or L-tryptophan beside antidepressants give positive finding of augmentation outcomes in boosting the anti-depressant response with some anti-depressant drugs.

According to Osiecki (2006), the co-factors magnesium, Calcium, B6, folic acid and iron are essential in the metabolism and conversion of Tryptophan to 5-HTP and B6, Zinc, Magnesium and vitamin to convert 5-HTP to serotonin (Figure 3).

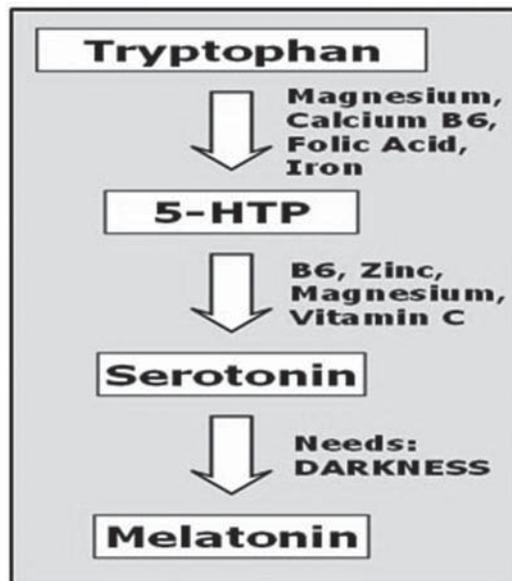


Figure 3 Formation 5-HTP and serotonin from tryptophan
 Source: By Meyers (2000).





OMEGA-3 FATTY ACIDS

Recently, new beneficial signs for omega-3 PUFA are suggested, for example management for specific types of mental illness, involving depressive disorders (Grosso et al., 2014). Depression might share with CVD some pathophysiological mechanisms, specifically endothelial dysfunction, increased manufacture of pro-inflammatory cytokines, and raises in level of plasma homocysteine (Severus et al., 2001). The factors, which affect omega-3 PUFA positive results on depression, might depend on their physiological rich content in the nervous system and their contribution in neuroplasticity in addition to neurogenesis (Bourre, 2004). Additionally, omega-3 PUFA anti-inflammatory ability might reduce inflammatory procedures happening in depression (Maes et al., 2009).

Omega-3 fatty anti-depressant action of acids occur through modulation of dopamine, norepinephrine, and serotonin re-uptake, synthesis, degradation and receptor binding; the improvement of cell membrane fluidity and anti-inflammatory effects (Sarris et al., 2012). A study done by Martins (2009), found that Eicosapentaenoic Acid (EPA) preparations, or those with more EPA to Docosahexaenoic Acid (DHA) ratios, possibly have a greater anti-depressant influence than DHA only.

METHODOLOGY

Searching for the literature

Aimed search: the literature was gained by searching library databases (MEDLINE (PubMed), Google Scholar, CINAHL, PsycINFO, Cochrane Library databases and Quartile databases). It is a summary of both conceptual and empirically published literature on the uses of nutraceuticals in depression management. A review of the literature was conducted to determine mechanisms of action of these nutraceuticals.

Search strategy: the keywords and phrases used in searching are CAM; Nutraceuticals; Depression; Anti-depressant; SAME; Folic acid; 5-hydroxytryptophan (5-HTP) Omega-3; Sustainability; Europe. The reference lists from published studies and reports were searched for additional sources. Number of specialised electronic Journals specialising in alternative medicine was searched. The overall search method shown discussion papers and information from consultation papers, which were examined to abstract evidence, related to the present literature review objectives.





Selecting the articles and review resources

Inclusion criteria: the inclusion criteria include articles (reviews, population, intervention of nutraceuticals in depression management and outcomes required).

Topics of interest: using of Nutraceuticals in mental disorders.

Evaluating the evidence: Last selection of articles was done by comprehensive review of each article, which was assessed by two persons to prevent errors and omissions.

DISCUSSION

Major Depressive Disorder (MDD) represents a big challenge for Europe public health because of its high prevalence and association with elevated debility and expenses for the individual, families and community. MDD exemplifies the first reason of absence from work and premature retirement in many European countries resulting in noticeable social and occupational impairment and reduced quality of life (Donohue and Pincus, 2007).

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) confirmed that depression often requiring multiple treatment trials as only a minority of people with MDD gets reduction through initial treatment with selective serotonin reuptake inhibitor (SSRI) (Fava et al., 2003).

The big range of abnormalities which found with MDD pathophysiology such as, neuroendocrinological changes, cytokine alterations and monoamine impairment, may be improved by using of adjunctive nutraceuticals through correcting the neurobiological mechanisms behind the disorder. Nutraceuticals like SAME, Folic acid, 5-HTP and omega-3 fatty acids may serve as possible treatments for improving response of SSRIs in patients with clinical depression. The above studied nutraceuticals have the potential to show significant benefits in improving depression in people non-responsive to contemporary antidepressants.

Although SAME seems more costly, considering its quickness of onset of the anti-depressant result and its side-effects profile, it may have a specific impact on in relations of treatment dosage and duration, drug gaining, inpatient and outpatient care, management of patients who discontinue therapy and time off work.

The usefulness of L-methylfolate is of great importance in depressed patients who have folate deficiency involving the patients who have folate deficiency due to the anti-convulsant mood stabilisers





**N.A. Khalifa
and E.A. Aljaaly**

administration and patients who their genotype coding to an enzyme which result in ineffective L-methylfolate formation. L-methylfolate regulates different monoamine neurotransmitter s activity through methylation. These complex mechanisms need functioning examination to resolve in what way the natural products, may participate to the treatment of depression.

Regarding 5-HT, the statistics proposes that 5-HT is efficient than placebo regarding the depression treatment but the proof was inadequate to be decisive and extra and bigger investigations are required to define if 5-HTP is really efficient in treating depression.

Omega-3 PUFA as therapeutic agents was effective in MDD patients in addition to depressive patients lacking MDD diagnosis. While the conducted studies on MDD patients or those on patients who have depressive symptoms but not rigorous evaluation by health specialists were joint together, an overall affirmative effect of omega-3 PUFA was bring into being.

Many nutraceuticals control several main pathways involved in depression pathogenesis and neurobiological pathways; however clinical trials usually focus on modulating just one or two neurochemicals. Nutrients commonly work together therefore it may not be obvious which nutrient components may be accountable for any found effect, however all studies confirmed the antidepressant evidence behind each component. One probable shortage of nutraceutical research is the use of isolated nutrients as opposed to multi-component formulas.

CONCLUSIONS, IMPLICATIONS AND RECOMMENDATIONS

- Observing the scale of the economic and social consequences and the costs of MDD, the benefits are great of efficient action to decrease occurrence and influence of MDD and to promote the mental health of the population as a whole.
- According to Friedli and Parsonage (2007), mental health augmentations can lead to better physical health results together with, reduced possibility of stroke and heart disease and reductions in alcohol and tobacco consumption and reduced obesity.





- With regard to the low incidence of complete recovery of patient treated with antidepressants, as a first-line treatment in addition to the side and unknown effect of long-standing use of these antidepressants, it is clearly essential upon mental experts to think about other ways of multiple treatment trials, consequently growth of more interventions is directly essential. One of the emerging ways to improve the non-or low-response to antidepressants is nutraceuticals usage.
- The positive anti-depressant action of nutraceuticals may provide an effective treatment option to improve the effectiveness of antidepressants and this may support the study of extra-complicated nutraceutical formulations for other medical disorders.
- With regard to the nutraceutical general safety application they must be used in a good safety profiles and therapeutic doses. However nutraceutical mechanism of action, bioavailability, and absorption are still questionable therefore further studies are indicated.
- In Europe they're a solid public health approach regarding mental health and CAM separately, (Figure 4). However there is a lack on CAM related to mental health so worthy information and significant research on complementary and traditional medicine (CAM) especially nutraceuticals in relation to mental health are essential for effective response, comprehensive decisions and evidence-based policy-making to achieve the European health policy targets 'Investing in Health' and upkeep sustainable healthcare systems.
- Complementary and traditional medicine (CAM) especially nutraceuticals and its relation to mental health can be included in the main stream policies like the National Programme for Improving Mental Health and Wellbeing in Scotland, Adolescents en Souffrance Report – France,... etc.
- World mental health day, which is usually held on 10th October, was formed by the World Health Organization to promote understanding and awareness about mental health issues with different theme each year. By making (Using CAM in mental health) a theme on the World mental health day will result in a solid public health approach through Europe, constructing on our combined knowledge, capability and expertis.

**The involvement
of nutraceuticals
to sustainable
healthcare in
Europe in the
context of MDD**





Figure 4 Examples of mental health and CAM activity in Europe



REFERENCES

- Ayuso-Mateos, J.L., Vázquez-Barquero, J.L., Dowrick, C., Lehtinen, V., Dalgard, O.S., Casey, P. and ODIN group (2001) 'Depressive disorders in Europe: Prevalence figures from the ODIN study', *British Journal of Psychiatry*, Vol. 179, No. 4, pp.308–316.
- Baldessarini, R.J. (1987) 'Neuropharmacology of S-adenosyl-L-methionine', *The American Journal of Medicine*, Vol. 83, No. 5A, pp.95–103.
- Belmaker, R.H. and Agam, G. (2008) 'Major depressive disorder', *The New England Journal of Medicine*, Vol. 358, No. 1, pp.55–68.
- Bottiglieri, T., Chary, T.K., Laundry, M., Carney, M.W., Godfrey, P., Toone, B.K. and Reynolds, E.H. (1988) 'Transmethylation in depression', *The Alabama Journal of Medical Sciences*, Vol. 25, No. 3, pp.296–301.
- Bourre, J.M. (2004) 'Roles of unsaturated fatty acids (especially omega-3 fatty acids) in the brain at various ages and during ageing', *The Journal of Nutrition Health and Aging*, Vol. 8, No. 3, pp.163–174.
- Byerley, W.F., Judd, L.L., Reimherr, F.W. and Grosser, B.I. (1987) '5-Hydroxytryptophan: A review of its antidepressant efficacy and adverse effects', *Journal of Clinical Psychopharmacology*, Vol. 7, No. 3, pp. 127–137.
- Cantoni, G.L. (1952) 'The nature of the active methyl donor formed enzymatically from L-methionine and adenosinetriphosphate', *Journal of the American Chemical Society*, Vol. 74, No. 11, pp.2942–2943.
- Coppen, A. and Bailey, J. (2000) 'Enhancement of the antidepressant action of fluoxetine by folic acid: A randomised, placebo controlled trial', *Journal of Affective Disorders*, Vol. 60, No. 2, pp.121–130.
- Coppen, A. and Bolander-Gouaille, C. (2005) 'Treatment of depression: Time to consider folic acid and vitamin B12', *Journal of Psychopharmacology*, Vol. 19, No. 1, pp.59–65.
- Curran, C., Knapp, M., McDaid, D., Tómasson, K. and The Mheen Group (2007) 'Mental health and employment: An overview of patterns and policies across the 17 MHEEN countries', *Journal of Mental Health*, Vol. 16, No. 2, pp.195–210.
- Donohue, J.M. and Pincus, H.A. (2007) 'Reducing the societal burden of depression: A review of economic costs, quality of care and effects of treatment', *PharmacoEconomics*, Vol. 25, No. 1, pp.7–24.
- Fava, M., Borus, J.S., Alpert, J.E., Nierenberg, A.A., Rosenbaum, J.F. and Bottiglieri, T. (1997) 'Folate, vitamin B12, and homocysteine in major depressive disorder', *The American Journal of Psychiatry*, Vol. 154, No. 3, pp.426–428.
- Fava, M. and Mischoulon, D. (2009) 'Folate in depression: Efficacy, safety, differences in formulations, and clinical issues', *Journal of Clinical Psychiatry*, Vol. 70, Supp. 5, pp.12–17.
- Fava, M., Rush, A.J., Trivedi, M.H., Nierenberg, A.A., Thase, M.E., Sackeim, H.A. and Kupfer, D.J. (2003) 'Background and rationale for the sequenced treatment alternatives to relieve depression (STAR*D) study', *Psychiatric Clinics of North America*, Vol. 26, No. 2, pp.457–494.
- Friedli, L. and Parsonage, M. (2007) *Mental Health Promotion: Building an Economic Case*, Belfast: Northern Ireland Association for Mental Health.
- Gören, J.L., Stoll, A.L., Damico, K.E., Sarmiento, I.A. and Cohen, B.M. (2004) 'Bio-availability and lack of toxicity of S-adenosyl-L-methionine (SAME) in humans', *Pharmacotherapy*, Vol. 24, No. 11, pp.1501–1507.
- Grosso, G., Galvano, F., Marventano, S., Malaguarnera, M., Bucolo, C., Drago, F. and Caraci, F. (2014) 'Omega-3 fatty acids and depression: Scientific evidence and biological mechanisms', *Oxidative Medicine and Cellular Longevity*, Article ID 313570, pp.1–16.
- Herman, P.M., Poindexter, B.L., Witt, C.M. and Eisenberg, D.M. (2012) 'Are complementary therapies and integrative care cost-effective? A systematic review of economic evaluations', *BMJ Open*, 2:e001046.
- Kalra, E.K. (2003) 'Nutraceutical-definition and introduction', *AAPS PharmScience*, Vol. 5, No. 3, pp.27–28.

The involvement of nutraceuticals to sustainable healthcare in Europe in the context of MDD





**N.A. Khalifa
and E.A. Aljaaly**

- Kresge, N., Tabor, H., Simoni, R.D. and Hill, R.L. (2005) 'An escape from Italy, the discovery of S-adenosylmethionine, and the biosynthesis of creatine by Giulio L. Cantoni. 1953', *Journal of Biological Chemistry*, Vol. 280, No. 38, p.e35.
- Maes, M., Yirmiya, R., Noraberg, J., Brene, S., Hibbeln, J., Perini, G. and Maj, M. (2009) 'The inflammatory & neurodegenerative (I&ND) hypothesis of depression: Leads for future research and new drug developments in depression', *Metabolic Brain Disease*, Vol. 24, No. 1, pp.27–53.
- Martins, J.G. (2009) 'EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials', *The Journal of the American College of Nutrition*, Vol. 28, No. 5, pp.525–542.
- Osiecki, H. (2006) *The Physician's Handbook of Clinical Nutrition*, 7th edition, Brisbane: Bio Concepts.
- Papakostas, G.I. (2009) 'Evidence for S-adenosyl-L-methionine (SAM-e) for the treatment of major depressive disorder', *Journal of Clinical Psychiatry*, Vol. 70, Supp. 5, pp.18–22.
- Salmans, S. (1997) *Depression: Questions You Have - Answers You Need*, People's Medical Society.
- Sarris, J., Mischoulon, D. and Schweitzer, I. (2012) 'Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression', *Journal of Clinical Psychiatry*, Vol. 73, No. 1, pp.81–86.
- Severus, W.E., Littman, A.B. and Stoll, A.L. (2001) 'Omega-3 fatty acids, homocysteine, and the increased risk of cardiovascular mortality in major depressive disorder', *Harvard Review of Psychiatry*, Vol. 9, No. 6, pp.280–293.
- Shaw, K., Turner, J. and Del Mar, C. (2002) 'Are tryptophan and 5-hydroxytryptophan effective treatments for depression? A meta-analysis', *Australian and New Zealand Journal of Psychiatry*, Vol. 36, No. 4, pp.488–491.
- Shippy, R.A., Mendez, D., Jones, K., Cerngul, I. and Karpiak, S.E. (2004) 'S-adenosyl-methionine (SAM-e) for the treatment of depression in people living with HIV/AIDS', *BMC Psychiatry*, Vol. 4, No. 38.
- Sobocki, P., Jonsson, B., Angst, J. and Rehnberg, C. (2006) 'Cost of depression in Europe', *Journal of Mental Health Policy and Economics*, Vol. 9, No. 2, pp.87–98.
- Meyers, S. (2000) 'Use of neurotransmitter precursors for treatment of depression', *Alternative Medicine Review*, Vol. 5, No. 1, pp.64–71.
- World Health Organization (2013) Available at: <http://www.euro.who.int/mentalhealth>.

BIOGRAPHICAL NOTES

Nahlaa A. Khalifa is Assistant Professor at the Clinical Nutrition Department, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia. She holds a PhD in food science and nutrition from Khartoum University in cooperation with Hannover University. She is the coordinator of evaluation and quality assurance program, Coordinator of undergraduate and postgraduate curriculum development, revision, Chairperson of academic advising committee, Consultant of the of academic accreditation committee. She has been awarded certificates for participation and attendance for health, community and educational missions. Being as invited speaker at many conferences and having published articles on food science and nutrition. Her main interests are in nutritional genomic and CAM. Her interests also lie in activation of modern information technology applications in teaching and research.





Dr. Elham A. Aljaaly is Saudi national. She is an Assistant Professor and the Head of the Clinical Nutrition Department at Medical Applied College, King Abdulaziz University in Jeddah, Saudi Arabia. She is the first graduate Saudi Dietitian from the Clinical Nutrition Programme in SA. Holding an MSc in Human Nutrition from University of Sheffield and PhD in Community Nutrition and Environmental Health from UCL, London. Two Post-Doctoral programmes in UK. She was a member of different committees in the Saudi Council for Health Specialist. She has published articles on nutritional status of adolescents and food advertising. Been an invited speaker at many national, regional and international conferences since 1986 to present.

**The involvement
of nutraceuticals
to sustainable
healthcare in
Europe in the
context of MDD**

