



• **High Lights**

- Vagus Nerve Stimulation for the management of depression
- Most fortified nutraceutical vitamins: standpoint from biochemistry, functionality, utilization strategies and medical genomics
- Dual darbox frame of a spacelike ruled surface and darbox approach to mannheim offsets of spacelike ruled surfaces

Natural Science and Discovery (www.natscidiscovery.com) is an international open access, peer-reviewed scientific research journal that provides rapid publication of articles in all disciplines of Natural science such as Physics, Mathematics, Chemistry, Biology, Engineering, Nanotechnology

The policy of top priority of NSD is to put forward and highlight medical innovations and inspiring patents

NSD offers an exceptionally fast publication schedule including prompt peer-review by the experts in the field and immediate publication upon acceptance.

The editorial board aims at reviewing the submitted articles as fast as possible and promptly including them in the forthcoming issues.

This journal is published under ethical publishing policy of international scientific ethical and publication rules. NSD supports the Open Access Initiative. Abstracts and full texts (HTML and PDF format) of all articles published by NSD are freely accessible to Researchers, Scientist, the Public and other users to view, download and share, immediately upon publication

Founder: Lycia Press

Concessionaire and Founding Editor : Zafer AKAN (Assoc. Prof. Dr.)

Publisher: Lycia Press, LONDON UK

Editor in Chief

Talha MUEZZINOGLU(Prof. Dr.) CBU, Faculty of Medicine Dept. of Urology, Manisa, TURKEY

Deputy Editor

Ozlem TOKUSOGLU (Assoc. Prof. Dr.) CBU, Faculty of Engineering Dept. of Food Engineering, Manisa, TURKEY

Honorary Editors

Prof. Dr. Gustavo Barbosa-CÁNOVAS, Washington State University, USA

Prof. Dr. Omer KUCUK, Emory University Winship Cancer Institute, USA

Prof. Dr. Peyami BATTAL, Yuzuncu Yil University, TR

All the financial and ethical rights of the journal are reserved for the private ownership of Lycia Press

Address: Lycia Press Inc., 4th Floor 86-90 Paul Street, EC2A 4NE, London, UK.

Phone: +44 0 203 322 3097

Email: [press \[at\] lycians.com](mailto:press@lycians.com)

Website: www.lycians.com

Editorial Board

Prof. Dr.	Talha MUEZZINOGLU	Celal Bayar University,TR (Editor in Chief)
Assoc. Prof. Dr.	Ozlem TOKUSOGLU	Celal Bayar University,TR (Deputy Editor)
Prof. Dr.	Dilek HEPERKAN	Istanbul Technical University (ITU) TR
Prof. Dr.	Atakan SUKATAR	Ege University, TR
Prof. Dr.	Arash KHAKE	Islamic Azad University, Iran
Dr.	Muhammet Burak BATIR	Islamic Azad University, Iran
Dr.	Omer KACAR	TUBITAK MAM TR
Asist. Prof. Dr.	Ozdemirhan SERCIN	University Libre de Bruxelles, Belgium
Prof. Dr.	Mahinur AKKAYA	Middle East Technical University TR
Asist. Prof. Dr.	Serife Kaymaksiz	Helmholtz-Institute Muenster, Germany
Prof. Dr.	Halit DEMIR	Yuzuncu Yil University, TR
Prof. Dr.	Ugur AVCIBASI	Celal Bayar University, TR
Asc. Prof. Dr.	Mehmet ONDER	Celal Bayar University,TR
Asist. Prof. Dr.	Evren ZIPLAR	Cankiri Karatekin University, TR
Prof. Dr.	Şafak ALPAY	Middle East Technical University, TR
Prof. Dr.	Cuneyt CAN	Middle East Technical University, TR
Assist. Prof. Dr.	Bahriye SIRAV	Gazi University, TR
Prof. Dr.	Iskender REYHANCAN	Istanbul Thecnical University, TR
Prof. Dr.	Mehmet Ali KORPINAR	Istanbul University, TR
Prof. Dr.	Tunaya KALKAN	Istanbul University, TR
Prof. Dr.	Mehmet MUTLU	TOBB Economy and Technology University, TR
Prof. Dr.	Erdal ÇOKÇA	Middle East Technical University TR
Prof. Dr.	Krishna R. REDDY	University of Illinois at Chicago, USA
Asc. Prof. Dr.	Yeliz YUKSELEN AKSOY	Dokuz Eylul University TR
Prof. Dr.	Jeffrey C. EVANS	Bucknell University, Pennsylvania, USA
Prof. Dr.	Adnan YAZICI	Middle East Technical Univ. (METU) TR
Prof. Dr.	Faruk BOZOGLU	Middle East Technical University, (METU) TR
Prof. Dr.	Kazutaka YAMAMOTO	National Food Research Institute (NFRI), JAPAN
Prof. Dr.	Halil VURAL	Hacettepe University, TR
Asc. Prof. Dr.	Brijesh Kumar TIWARI	Manchester Metropolitan University, Manchester, UK
Prof. Dr.	Tayfur OZTURK	Middle East Technical Univ. (METU) TR
Asist. Prof. Dr.	Balati KUERBANJIANG	University of York, York, UK
Prof. Dr	Rahmi GUCLU	Yıldız Technical University, TR

Statistical Editor

Prof. Dr. Siddik KESKİN YYU Faculty of Medicine, Dept. of Medical Statistics

Language Editor

Asist. Prof. Dr. Hakan ERGİN Istanbul University, Dept. of Foreign Languages

Editorial Office

Typist Office Lycia Press office@lycians.com
Web Web Lycia Press info@lycians.com

Instruction for Authors

- NSD Publications uses CrossCheck's iThenticate software to detect instances of similarity in submitted manuscripts. In publishing only original research, NSD is committed to deterring plagiarism, including self-plagiarism. Your manuscript may be screened for similarity to published material.
- Dear Authors, please load just these three file to manuscript submission system
- Title Page Sample
- Manuscript Sample
- Copyright Transfer Form
- **Manuscript Preparation:**
- **1.Cover letter**
- a- A statement that the manuscript has been read and approved by all the authors.
- b- Approval of all the authors regarding the order in which their names have appeared.
- c- That each author confirms the manuscript represents honest work.
- d- The name, address, and telephone number of the corresponding author who is responsible for communicating with other authors about revisions and final approval.
- e- The letter should give any additional information that may be helpful to the editor, such as the type or format of the article. If the manuscript has been submitted previously to another journal or in another language, it is helpful to include the previous editor's and reviewers' comments with the submitted manuscript, along with the authors' responses to those comments. Submitting previous evaluatory review of another journal accelerates the review process.
- f- For accepted manuscripts, the authors are requested to fill and sign the journal's cover letter to express their consent for its publication.
- g- To reproduce published material, to use illustrations or tables or report information about identifiable people, the author should submit a copy of the permission with the manuscript to the journal.
- **2.Top Ethic Committee Approval**
- Inclusion of the approval letter from the relevant Ethics Committee or Institution's Review Board regarding the research protocol and the rights of the subjects (if applicable to the study)
- **3.Top Consent Form**
- Attach a copy of the consent form to the letter, if applicable. Consent forms would be evaluated by the Ethics Committee and then signed by the participant.
- **4.Top RCT or NCT Registration**
- Emailing the letter denoting registration of RCTs or NCTs in domestic or international databases (The trial's registration number needs to be mentioned, too).
- **5. Manuscripts submitted in English**, must be type written, double-spaced, on good quality A4 paper, or paper of similar format. Authors are requested to reserve margins of at least 2.5cm all around the paper. Original drawings of photos, tables and figures should be furnished together with the manuscripts.
- **6. Manuscripts should be kept to a minimum length** and should be subdivided into labeled sections (Title page, Abstract, Keywords, Introduction, Materials and Methods, Results, Discussion, Conclusion, Acknowledgement, and References).
- **7. A title page is to be provided** and should include the title of the article, authors' names with full first name (with degrees), authors' affiliation, suggested running title and corresponding author. The affiliation should comprise the department, institution (usually university or company), city and state (or nation). The suggested running title should be less than 50 characters (including spaces) and should comprise the article title or an abbreviated version thereof. For office purposes, the title page should include the name and complete mailing address, telephone and fax number, and email of the one author designated to review proofs.
- **8. An abstract no longer than 250** words for reviews and research articles is to be provided as the second page. Abstract should be structured as objective(s) (including purpose setting), materials and methods, results, and conclusion.
- **9. A list of 3-8 keywords**, is to be provided directly below the abstract. Keywords should express the precise content of the manuscript, as they are used for indexing purposes. Provide abbreviations and nomenclature list in an alphabetical order and non-standard abbreviations contained in the manuscript (excluding references) with definitions after the keywords. Use abbreviations sparingly and only when necessary to save space, and to avoid repeating long chemical names or therapeutic regimes. In a figure or table, define the abbreviations used in a footnote.
- **10. Tables in limited numbers** should be self- explanatory, clearly arranged, and supplemental to the text. The captions should be placed above.
- **11. Figures should be utilized** only if they augment understandability of the text. The captions should be placed below. Drawings and graphs should be professionally prepared in deep black and submitted as glossy, black and white clean Photostats. Professionally designed computer generated graphs with a minimum of 300 DPI laser printer output is preferable. Color photographs are welcomed.
- **12. The same data** should not be presented in tables, figures and text, simultaneously.
- **13. NSD uses Vancouver referencing Style.** References in limited numbers and up-to-dated must be numbered consecutively in order of citation in the text (number in parentheses). Print surnames and initials of all authors when there are six or less. In the case of seven or more authors, the names of the first six authors followed by et al. should be listed.
- Please check all references with EndNote referencing System. Please check out and Download Vancouver Endnote Style.

Instruction for Authors

• **TYPE OF ARTICLES**

• **Editorial :**

- Editorial is Opinion piece, policy statement, or general commentary, typically written by staff of the publication (The similar value "article-commentary" is reserved for a commentary on a specific article or articles, which is written by an author with a contrasting position, not an editor or other publication staff.)

• **Letters to the Editor** about a recent journal article :

- Letters referring to a recent article in this journal must be received within three months of its publication. For example, a letter referring to an article published in the January issue must be submitted online no later than March 31st. Letters submitted after the allowed time will not be considered.

- The text, not including references, must not exceed 700 words. A maximum of three authors and 10 references are allowed. Neither tables nor figures are allowed.

• Letters to the Editor NOT referring to a recent journal article :

- Original research that is of interest but does not fulfill all the requirements needed for publication as a full-length manuscript can be submitted as a letter to the editor. The letter must have a title and a maximum of three authors.
- The text, not including references, tables, figures or legends must not exceed 700 words. No more than 10 references and either one table or one figure are allowed.
- Word Count Limit: Letters should contain 500 - 700 words, maximum number of references is 10, maximum Number of illustrations/Tables is 1.

• **Original :**

- The content of the paper must justify its length. For reports of original investigative work, traditional division into sections is required: Title, Keywords, Addresses and which author address for correspondence, Structured abstract, Background, Objectives, Materials/Patients and Methods, Results, Discussion, References and Acknowledgements, Legends for display items (Figures and Tables).
- Research articles should contain 2500 - 3500 words, maximum number of references is 35, maximum Number of illustrations/Tables is 5.

• **Review Article:**

- Review Articles should contain 3500 - 4000 words, maximum number of references is 50, maximum number of illustrations/Tables is 5. In a review article both abstract and text of the manuscript, include following items:
- 1) Context: Include 1 or 2 sentences describing the clinical question or issue and its importance in clinical practice or public health.
- 2) Evidence Acquisition: Describe the data sources used, including the search strategies, years searched, and other sources of material, such as subsequent reference searches of retrieved articles. Explain the methods used for quality assessment and the inclusion of identified articles.
- 3) Results: Address the major findings of the review of the clinical issue or topic in an evidence-based, objective, and balanced fashion, emphasizing the highest-quality evidence available.
- 4) Conclusions: Clearly state the conclusions to answer the questions posed if applicable, basing the conclusions on available evidence, and emphasize how clinicians should apply current knowledge.

• **Hypothesis:**

- Hypothesis should not exceed 2000 words with a structured abstract of 200 words maximum. Hypothesis should comprise sections of Background, Objectives, Materials & Methods, Predicted Results with not more than 2 tables or figures and up to 20 references

• **Brief Report :**

- Brief Reports should contain 1000 - 2000 words with a structured abstract of 200 words maximum. Short reports should comprise sections of Background, Objectives, Materials & Methods, Results and Discussion with not more than 2 tables or figures and up to 20 references.

• **Short Communication :**

- Short Communication, follow the instructions for original articles, except that the total word number of the main text (excluding references, tables and figure legends) is limited to 2000 with no more than 2 figures and/or tables and no more than 15 references. An abstract, not exceeding 150 words, should be presented at the beginning of the article.

• **News :**

- News should contain 1000 - 2000 words with a structured abstract of 200 words maximum. News should comprise sections of Background, Objectives, Materials & Methods, Results and Discussion with not more than 2 tables or figures and up to 20 references.

• **Submission and Review Process :**

- Manuscripts must be written in English (use consistently either British or American spelling) and must be submitted online. To submit, go to <http://natscidiscovery.com> Full instructions for submission are detailed on submission system.

Instruction for Authors

- **C. General Consideration:**
- **1. Peer review process:** All submissions will be reviewed anonymously by at least two independent referees. All manuscripts will be acknowledged upon presenting to the Journal office, provided that all stated requirements are met. Authors are encouraged to suggest names of two expert reviewers, but selection remains a prerogative of the Editor. The whole review process depends on receiving referees comments and revising the manuscripts based on these comments to the author. On receipt of the revised article from the author, and after final approving by referees, the letter of acceptance is issued to the author. Authors have the right to communicate to the editor if they do not wish their manuscript to be reviewed by a particular reviewer because of potential conflicts of interest. No article is rejected unless negative comments are received from at least two reviewers.
- **2. Conflicts of interest:** Authors should disclose, at the time of submission, information on financial conflicts of interest or other interests that may influence the manuscript. Authors should declare sources of funding for the work undertaken.
- **3. The Journal's Policy on Plagiarism:** Any practice of plagiarism will not be tolerated by the journal regarding submitted manuscripts. Non-identifiable quoted segments of articles or close paraphrases from other author/s or even submitting the author's previously published work are known as the act of plagiarism by this journal unless proper use of quotations or paraphrasing with decent citation or referencing are in place. Heavy use of one or a couple of articles is discouraged, even if paraphrased fully. Advertent practice of plagiarism will abort reviewing process or later submission to this journal. All submitted articles will evaluate by iThenticate software belonged to cross check for stop any plagiarism and improve publication quality.
- **4. Ethical consent:** All submitted articles involving human experiments should be performed only in accordance with the ethical standards provided by the responsible committee of the institution and in accordance with the Declaration of Helsinki (as revised in Edinburgh 2000), available at <http://www.wma.net/en/30publications/10policies/b3/index.html>. Papers describing animal experiments can be accepted for publication only if the experiment conforms the National Institute of Health Guide (National Institute of Health Publications No. 80-23, Revised 1978) for the care and use of Laboratory Animals for experimental procedure. Authors must provide a full description of their anesthetics and surgical procedures. All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming the informed consent was obtained from each subject or subject's guardian. All animal or human studies should be used after approval of the experimental protocol by a local ethics committee
- **5. Acknowledgements:** Contributors: In acknowledgement section, name people for their contributions or their permission to reproduce their published material, to use their illustrations or provide information about them- try to fully name people who have helped from the conception of the idea to adoption of the hypothesis, to finalization of the study, etc., earnestly. Statement of financial support: Aside from the title page, state any financial or other relationships that might lead to a conflict of interest.
- **6. Copyright:** Please complete copyright form and send via email to editor. Download NSD Copyright Form
- **7. Disposal of material:** Once published, all copies of the manuscript, correspondence and artwork will be held for 6 months before disposal.
- **8. Creative Commons License**
- This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.
- **9. Once a manuscript** is accepted for publication it will be provided with a registered DOI number following the acceptance decision. Manuscripts accepted for publication by the MSD will be published as ahead of print articles prior to the printing date of their scheduled issue. Corresponding author will be provided with a PDF Proof by the publisher once the production process of an accepted manuscript is over.
- **10. Briefly Sections of NSD article:**
- Sections of article should insert into just one word document and uploaded to NSD submission system as manuscript document. Title page will detach from manuscript by NSD editors and manuscript will forward to referees without title page due to double blinded review rules.

Instruction for Authors

- **Brief Section of NSD**
- **1-Title Page Section**
- Article Type:
- Title of Article:
- Name Surname of Author1, Name Surname of Author2, ...
- 1 Author Name Surname, Affiliation, e-mail address
- 2 Author Name Surname, Affiliation, e-mail address
- *Corresponding Author :
- Author Name Surname, Affiliation, Address, Phone, Fax, E-mail address,
- Corresponding Author should upload all file
- **2-Manuscript Section**
- Abstract (Objective: Methods: Results: Conclusion: "200-250 words and Key words)
- Introduction, Material and Methods, Statistics, Results, Discussion, Conclusion Acknowledgement, References.
- **3-Table and Figures Section**
- Tables and Legends, Figures and Legends should be inserted end of the references
- **Article Processing Charge**
- NSD is a non-profit Scientific Journal Platform; however, it uses professional services such as Language Editing, DOI, domain and hosting, iThenticate Plagiarism or similarity detection Detection Software. All of these professional services are used for all the article processes and an inevitable cost arises with this.
- Unfortunately, like most open journals, fees of the publication with NSD are charged to Authors. Payment is under the responsibilities of corresponding Author(s). NSD does not charge any fee during the submission period. However, after the peer-review process, a non-refundable charge (100 USD) for each accepted manuscript must be paid by the author(s) via NSD's official PayPal account. An invoice will be sent for each accepted manuscript to corresponding author(s).
- Following with completion of payment procedure, the galey proof and acceptance letter of article will be send to authors for last check.
- Preperation of articles in PDF and HTMLformat is covered by Lycia Press Inc. (www.lycians.com) and Article Processing Charges paid to Lycia Press Inc. (www.lycians.com)

Contents

Editorial

- 1 Welcome message from the Editor-in-chief
Talha Muezzinoglu
Natural Science and Discovery, March 2015, 1(1):1

Letter to Editor

- 2 Vagus Nerve Stimulation for the management of depression: Rationale, anatomical and physiological basis of efficacy and future prospects
Metin Tulgar, Erol Ozan, Zafer Akan
Natural Science and Discovery, March 2015, 1(1):2

Review Articles

- 3 Most fortified nutraceutical vitamins: standpoint from biochemistry, functionality, utilization strategies and medical genomics
Ozlem Tokusoglu, Talha Muezzinoglu
Natural Science and Discovery, March 2015, 1(1):3-28

Original Articles

- 4 Dual darboux frame of a spacelike ruled surface and darboux approach to mannheim offsets of spacelike ruled surfaces
Mehmet Onder, H. Huseyin Ugurlu
Natural Science and Discovery, March 2015, 1(1):29-41

Welcome message from the Editor-in-chief

Talha Muezzinoğlu^{1*}

Dear authors, reviewers and readers of Natural Science and Discovery

It gives me great pleasure to welcome you to the first edition of Natural Science and Discovery for which I have acted as Editor in Chief.

Natural Science and Discovery is an international open access, peer-reviewed scientific research journal that provides rapid publication of articles in all disciplines of Natural science such as Physics, Chemistry, Biology, Mathematics, and their connected Applied Sciences such as Engineering including Biomedical Engineering, Civil Engineering, Food Engineering, Industrial Engineering, Mechanical Engineering, Material Science and Nanotechnology

I am very aware of the responsibilities that the editor's role entails, and I approach my new role with so excitement. I would like to point out that the policy of top priority of NSD is especially to put forward and to reveal the innovations and inspiring outputs for natural science and engineering.. NSD offers an exceptionally fast publication schedule including prompt peer-review by the experts in the field and immediate publication upon acceptance. Not only my deputy editorial concept but also the all editorial board aims the fast reviewing and evaluation of the submitted articles for the forthcoming issues. Our journal distinction is to make difference in this inspection point.

Natural Science and Discovery journal will continue to publish high quality researches on basic sciences and applied sciences.. Original research articles form the bulk of the content, with systematic reviews an important sub-section. We will encourage all authors to work to these standards. Such emphasis on methodological rigour is vital to ensure that conclusions reached from publications contained in the journal are valid and reliable.

Peer review processing remains a vital component of our assessment of submitted articles to NSD. I would like to say that there is strong consensus that accepted articles are often improved by peer review after referees' comments and criticisms are dealt with; this explicit appraisal process also helps to engender trust of the reader. It is predicated that the criticisms of evaluating process containing publication delaying, unreliability of decision making as overly conservative approach. Besides, weaknesses can be managed by an effective and active editorial office, and I believe they are outweighed by the benefits.

Lastly I should thank all our submitting authors, who have toiled in the production of their work, and have chosen Natural Science and Discovery as the journal they would like to publish in.

Have a great Publishing with NSD...

Professor Dr Talha Muezzinoglu

Editor in Chief, NSD.

Copyright © 2014 The Author(s); This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. All Rights reserved by international journal of Natural Science and Discovery and Lycians Press Inc.

Vagus Nerve Stimulation for the management of depression: Rationale, anatomical and physiological basis of efficacy and future prospects

Metin Tulgar¹, Erol Ozan^{2*}, Zafer Akan³

Dear Editor,

Treatment-resistant depression (TRD) is a major public health concern due to its high costs to society. One of the novel approaches for the treatment of depression is the Vagus Nerve Stimulation (VNS). Therapeutic brain stimulation through delivery of pulsed electrical impulses to the left cervical vagus nerve now has established safety and efficacy as an adjunct treatment for medication-resistant epilepsy (1).

Vagus nerve stimulation therapy is US FDA approved for the adjunctive treatment of epilepsy and has also been applied for the medication resistant depression (2-6). Owing to its novel route into the brain, it has no drug-drug interactions or systemic side effects. This treatment also appears to have high long term tolerability in patients, with low rates of patients relapsing on Vagus nerve stimulation or becoming tolerant.

However, alongside the excitement and enthusiasm for this new treatment, a lack of Class I evidence of efficacy in treatment depression is currently slowing down adoption by psychiatrists.

Much more research is needed regarding exactly how to refine and deliver the electrical pulses and how this differentially affects brain function in health and disease.

In this clinical study, 10 patients (7 women, 3 men) who have diagnosis of major depression, the ages of patients are between 31 and 44. After two years follow up, the patients' Hamilton depression scores have been improved significantly.

In the present literature, heavy cases are advised to be excluded (7). Very interestingly, in this study a 44 year old lady, who was repeatedly talking about suicide, soon after the activation of the vagal nerve implant rescued.

As to our first prelaminary report about Vagus nerve stimulators and management of depression indicate that, VNS treatment may be an alternative to treatment for major depression patients.

References

1. Tulgar M, Bilgin S, Yildirim A. The Human Body's Own Language to be Considered for Safe and Effective Neurostimulation. *Neurol Ther.* 2012; 1:2-7.
2. Rush AJ, George MS, Sackeim A, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. *Biol Psychiatry.* 2000;47(4):276-286
3. Sackeim HA, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology* 2001;25(5):713-728
4. Schlaepfer TE, Frick C, Zobel A, et al. Vagus nerve stimulation for depression: efficacy and safety in a European study. *Psychol Med.* 2008; 38(5):651-61.
5. Sperling W, Reulbach U, Kornhuber J. Clinical benefits and cost effectiveness of vagus nerve stimulation in a long-term treatment of patients with major depression. *Pharmacopsychiatry* 2009;42(3):85-88.
6. Nierenberg AA, Alpert JE, Gardner-Schuster EE, et al. Vagus nerve stimulation: 2-year outcomes for bipolar versus unipolar treatment-resistant depression. *Biol Psychiatry.* 2008; 64(6):455-60.

Copyright © 2014 The Author(s); This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Received: 05-03-2015, Accepted 10-03-2015, Available Online 30-03-2015

¹Yuzuncu Yil University School of Medicine Dept. of Biophysics Van, Turkey

²Celal Bayar University School of Medicine Dept. of Psychiatry, Manisa, Turkey

³Celal Bayar University School of Medicine Dept. of Biophysics, Manisa, Turkey

*Corresponding Author: Erol Ozan E-mail: erolozan@gmail.com

Most fortified nutraceutical vitamins: standpoint from biochemistry, functionality, utilization strategies and medical genomics

Ozlem Tokusoglu^{1*}, Talha Muezzinoglu²

Abstract

Nutraceutical vitamins are micronutrients of foods and beverages that play an essential role in food science and technology. Most fortified vitamin A, E, D and folic acid as antioxidative defence system components and that of with gene regulation functions have been considered. Up-to-date scientific overview of the biochemistry, functionality, utilization strategies and human genomics of above-mentioned most fortified nutraceutical vitamins were emphasized

Keywords: Nutraceutical vitamins, vitamin A, E, D, Folic acid

CONTENT

1. The unified introduction to food vitamins from a biochemical and human genomics standpoint
2. Up-to-date scientific overview of the most fortified vitamins as antioxidative defense system components and as factors involved in genetic regulation
 - 2.1. The Biochemistry, Functionality and DRI of Antioxidant Vitamin E
 - 2.2. The Biochemistry, Functionality and DRI of Vitamin A and Carotenoids
 - 2.3. The Biochemistry, Functionality and DRI of Vitamin D
 - 2.4. Utilization Strategies of Fortified Vitamin A,D,E
 - 2.5. The Biochemistry, Functionality and DRI of Folic Acid
3. The interactions between most fortified & dietary bioactive vitamins and genomics/vitamin-dependent genes: Nutritional,metabolic and medical aspects
4. References

1. Introduction

1. The unified introduction to food vitamins from a biochemical and human genomics standpoint

Vitamins are micronutrients of foods and beverages that play an essential role in human nutrition. The occurrence of the vitamins in the various groups of food is related to their water or fat-solubility. They comprise a diverse group of organic compounds that are nutritionally essential minor components.

Vitamin function *in vivo* in several ways, including (a) as coenzymes or their precursors (niacin, thiamin, riboflavin, vitamin B₆, vitamin B₁₂, biotin, pantothenic acid, and folate); (b) as components of the antioxidative defense system (ascorbic acid, certain carotenoids and vitamin E); (c) as factors involved in genetic regulation (vitamin A and vitamin D, vitamin B₆, folate) is precious for human health and nutrition (1,2) (Figure 1.1.1.).

Food is a very complex matrix made up of lots of many individual components including fat and water soluble vitamins that a group of essential organic molecules. Fat soluble (A,D,E,K) and water soluble vitamins (B group, C, biotin, pantothenic acid) in foods have been categorized as above-mentioned three groups from a biochemical standpoint (Figure 1.1.1.).

The organism must obtain from exogenous sources and that is essential for the organism's normal metabolic and physiological functions (3). The elimination of vitamins from the diet must result in a more-or-less clearly defined deficiency disease, and restoration must cure or prevent that deficiency disease.

With developing of functional foods, nutraceuticals and dietary patterns, “dietary nutriome” (nutrient profile and composition) and genome health maintenance has been improved. Nutrigenomics based on genome healths is an emerging and recent important field of food nutritional science due to it is increasingly evident that optimal concentration of micronutrients for the prevention of genome damage is dependent upon genetic polymorphisms that alter the gene function involved directly or indirectly in DNA repair and metabolism. It has shown that above-average intake of certain micronutrients (i.e. vitamin E, retinol, folate, vitamin B₆) is associated with a reduced genome damage rate measured using the micronucleus assay (4).

In this chapter context, most fortified vitamins as antioxidative defence system components and vitamins with gene regulation functions have been considered

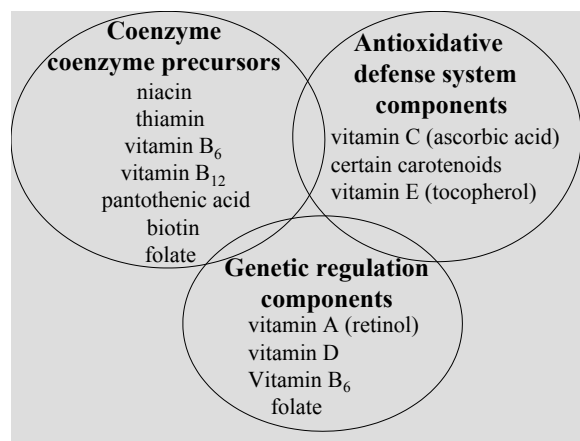


Figure 1.1.1. Vitamin function *in vivo*

2. Preliminaries

2. Up-to-date scientific overview of the most fortified vitamins as antioxidative defense system components and as factors involved in genetic regulation

Foods and beverages are fortified with micronutrients and bioactive compounds to prevent deficiencies or to provide additional health effects (106). The first step in the establishment of a fortification process must be the determination of the extent and the magnitude of the vitamin deficiency, as well as its distribution among the different ecological regions, socioeconomic levels and age groups.

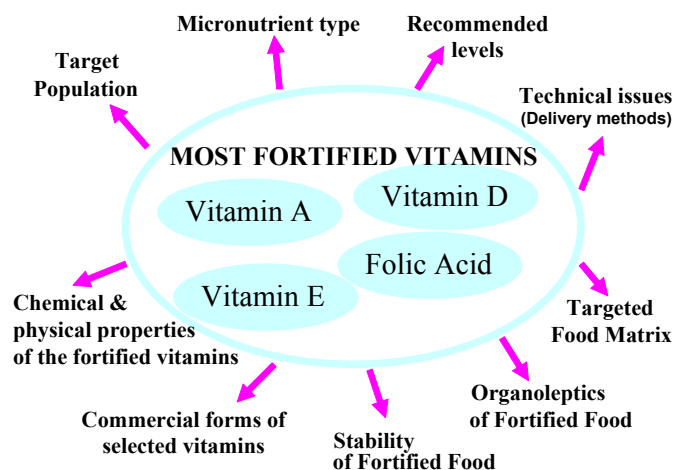


Figure 2.2.1. Possible Factors on Most Fortified Vitamins

It is reported that the most fortified vitamins are vitamin E, A, D and folic acid. Figure 2.2.1. shows the possible factors on most fortified vitamins for human nutrition. It is noteworthy that the target population, fortified vitamin type as micronutrient, recommended levels of vitamins, technical issues such as vitamin delivering to targeted foods, chemical and physical properties of the fortified vitamins, commercial forms of selected vitamins, targeted food matrix, stability of fortified food, organoleptic quality of fortified food are extremely important for fortification strategy (Figure 2.2.1.).

Antioxidants quench free radicals via donating the phenolic H and an electron. They exhibit variable degrees of efficiency for protection of human cells. Vitamin E (tocopherols and tocotrienols), vitamin C (ascorbic acid) and certain carotenoids (β -carotene), when not esterified, have the ability to act as antioxidants (1). Recently, a great interest has been focused on antioxidant vitamins in foods, particularly owing to their

likely role in the prevention of coronary heart diseases and cancer (5-7). Vitamins especially vitamin A and vitamin D and folate as factors involved in genetic regulation for human genomics.

Fortificated vitamins as micronutrient should be safe for human nutrition and tolerable upper intake levels (ULs) should be established. After fortification, the use of health claims on products is thought to result in better marketing (108).

The effect of fortification is both fast and broad. When a staple food which is consumed regularly by the majority of the population is utilized as a fortification vehicle, high population coverage can be easily accomplished. The combinations of micronutrients increase the cost-effectiveness of fortification (108).

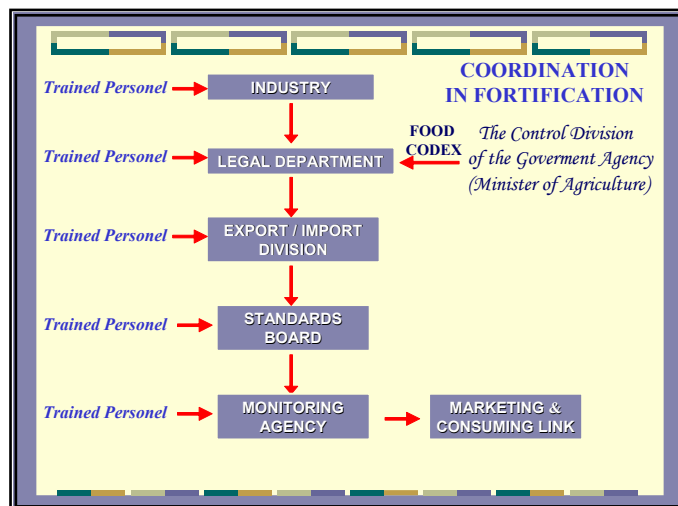


Figure 8.2.2. The Coordination Strategies in Fortification (Source: Adopted from Tokuşoğlu, 2006. *Fortification Criteria of Vegetable Oils and Margarines with Alpha-Tocopherol and Tocopheryl Acetate: The Regulations on Vitamin E Labeling*. Lecture. In World Conference and Exhibition on Oilseed and Vegetable Oil Utilization, Processing, By-Products, Biodiesel, Specialty and Functional Oils, and New Applications & Technologies 14-16 August 2006, Istanbul)

Figure 2.2.2. demonstrates the coordination strategies in fortification. Prior to Food codex by The Control Division of the Government Agency (generally Minister of Agriculture) are received to legal department, industrial manufacturing of fortified foods are performed. Then fortification with trained personel is controlled export-import division, standard boards, monitoring agency, respectively and evaluated via marketing and consuming link (107).

The biochemistry, functionality and dietary reference intakes (DRI) of most fortified vitamins as antioxidative defense system components vitamin E, certain carotenoids and as factors involved in genetic regulation components vitamin A, vitamin D and folic acid were focused on.

2.2.1. The Biochemistry, Functionality and Dietary Reference Intakes of Antioxidant Vitamin E

Vitamin E is generic term that represents four tocopherol and four tocotrienols of varying biological potency. "Tocopherol" term correctly refers to the methyl-substituted derivatives of tocol (8) (Figure 2.2.1.1.).

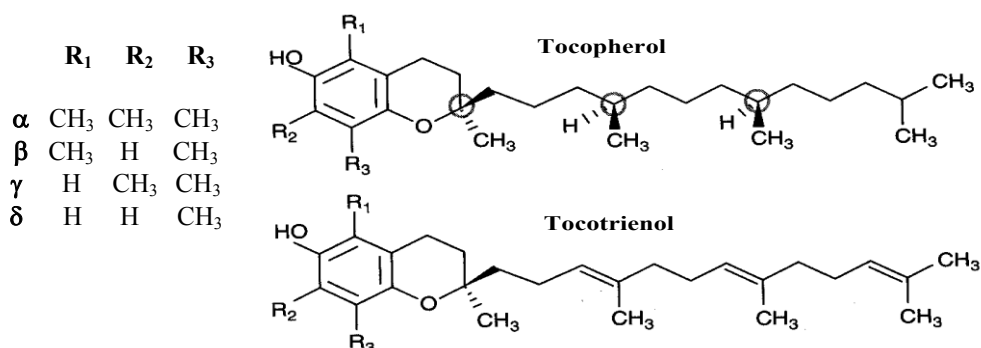


Figure 8.2.1.1. Vitamin E structures (8)

Tocopherols occur widely in nature and are monophenolic antioxidants that are composed of eight different compounds belonging to two families, namely tocols and tocotrienols, referred to as α , β , γ or δ , depending on the number and the position of methyl groups of attached to the chromane rings (8.9) (Figure 2.2.)

Vitamin E is a generic term which includes, in decreasing order of physiological activity alfa (α -), beta (β -), gamma (γ -), and delta (δ -) tocopherols (α -T, β -T, γ -T, δ -T) (2). The most biologically active is α -tocopherol, but β -, γ -, and δ -tocopherols also have important biologic activity (13).

The major lipophilic antioxidant is vitamin E especially α -tocopherol, that inhibits peroxidation of polyunsaturated fatty acids (PUFAs) in cell membranes and it is a liposoluble vitamin with an antioxidant capacity, reacting with peroxy radicals and other free radicals (22). Vitamin E that is a potent peroxy radical scavenger and especially protects PUFA within phospholipids of cellular biological membranes and in plasma proteins. All vitamin E forms act as lipid soluble chain-breaking antioxidants and prevent the oxidation of fats and vitamin A (8,9).

The biological activity of vitamin E is thought to reflect its ability to quench oxygen- and carbon-based free radicals and thus to protect the organism from oxidative damage. Vitamin E is a dietary lipid that is essential for vertebrate health and fertility (10,13).

Epidemiological and numerous studies indicated that diet including tocopherols prevent the risk of cardiovascular diseases and cancer (16-18,21). Tocopherols has also been associated with a reduction in the risk of disorders connected to free radicals, such as atherosclerosis, cancer, cataracts and cell damage connected to ischaemia and reperfusion (19,20).

Clinical studies to demonstrate that vitamin E supplements can help to delay or even prevent coronary heart disease. It is also stated that vitamin E can help prevent prostate cancer (11). According to trial concerning vitamin E and cancer; twelve studies, which included 167025 participants, met the inclusion criteria. There were no statistically significant differences in total mortality [relative risk, 0.99; 95% CI, 0.96-1.03] among the different groups of patients included in this meta-analysis (11). It was found that vitamin E was associated with a significant reduction in the incidence of prostate cancer [relative risk, 0.85; 95% CI, 0.73-0.96, number needed to treat=500] (11).

Recent reports suggest that vitamin E may also display gene expression modulation activities. It is shown that treatment of cultured hepatocytes with (RRR)- α -tocopherol alters the expression of multiple genes and that these effects are distinct from those elicited by another antioxidant (12). It was performed that genes modulated by vitamin E include those that encode key enzymes in the cholesterol biosynthetic pathway (12). These observations indicate that vitamin E possesses novel transcriptional activities that affect fundamental biological processes.

Dietary Value of Vitamin E

1 IU of vitamin E is the activity of 1 mg of all-*rac*- α -tocopheryl acetate, but the activity is nowadays expressed a milligrams of α -tocopherol equivalents (14). For determining the total vitamin E activity of mixed diets in the USA, total mg of α -tocopherol equivalents was calculated. The mg of β -tocopherol, γ -tocopherol and β -tocopherol-3 can be multiplied by factors of 0.5, 0.1, and 0.3, respectively, and added to the mg of α -tocopherol to give the total mg of α -tocopherol equivalents (14).

$$\Sigma \text{mg } T.\text{equivalents} = 0.5(\beta\text{-T}) + 0.1(\gamma\text{-T}) + 0.3(\beta\text{-T-3}) + (\alpha\text{-T}) \quad (14)$$

Especially, the best dietary sources of vitamin E are edible vegetable oils but some cereals and infant formula are the good sources of vitamin E (Table 2.2.1.1- 2.2.1.3). α -tocopherol level of vegetable oils is about 60 percent of the their total tocopherols. Oil processing (refining, deodorizing), boiling of vegetables, baking or storage of foods can result in substantial tocopherol losses (2).

Infant milk formulas can be considered as one of the principal sources of tocopherols (vitamin E) during this crucial step of baby life. Infant formulas contain tocopherols arising from oil combination used in manufacturing process and it may not adequate for baby nutrition. Tocopherols are added to the infant formulas either to improve the vitamin E supply or to prevent lipid oxidation. For this purpose, the use of α -T (D and DL) and α -tocopherol acetate (α -TAc) (D and DL) is permitted by law (15,23). It is reported that the mean contents of α -, γ - and δ - tocopherol were in powdered 'starting' and 'follow-on' infant formulas as 15.7-16.6; 2.4-3.9 and 0.11-1.35 mg/100 g, respectively (15,30). Tocopherols which have antiatherosclerotic, anticarcinogen, and antisterilitic effects are strong antioxidants for the body. Tocopherol level is inadequate in premature infants and hemolytic anaemia may develop if it is also deficient in breast milk and if the infant is fed with formulas containing rich levels of polyunsaturated fatty acids (PUFAs) but low levels of vitamin E. In this context, the vitamin E composition of breast milk is important (31, 32).

Transplacental delivery of vitamin E to the fetus is limited, although total body stores increase in late gestation, together with the amount of the adipose tissue. Vitamin E is higher in colostrum than mature milk, which contains approximately 3 IU/L (1 IU=1.5 mg). Thus, mature human milk comes close to meeting the DRI of 3 IU per day of vitamin E. Supplementation of the maternal diet with relatively large amounts of vitamin E is necessary to increase the milk levels of this vitamin (31).

Table 2.2.1.1. Vitamin E contents of some fats & oils (as mg/100g)	Table 2.2.1.2. Vitamin E contents of and cereals & cereal products and nuts (as mg/100g)*	Table 2.2.1.3. Vitamin E contents of and some consumed foods (as mg/100g)
<p>FATS & OILS</p> <p>soybean 96-115 palm oil 89-117 corn oi 78-109 cottonseed oil 78 sesame oil 82-137 canola 65 sunflower oil 47-67 safflower 49-80 rice bran 9-160 peanut 37 cocoa butter 20 olive oil 5.1 butter 1.1-2.3 coconut 1.0-3.6</p> <p><i>Source: Eitenmiller,1997 ; Tokuşođlu et.al.,2003</i></p>	<p>CEREALS</p> <p>wheat 7.0-10.0 rye 2.2-5.7 oat 1.8-4.9 rice (with hulls) 2.9 rice (polished) 0.4 corn 9.5 whole wheat meal 3.7 wheat flour 2.3-5.4 whole rye meal 2.0-4.5 white bread 2.15 crisp bread 4.0 whole rye bread 1.3 corn grits 1.17 oat flakes 3.85 corn flakes 0.43</p> <p>NUTS (α-Toc.)</p> <p>almond 11.0 hazelnut 6.5 peanut 3.5 pistachio 1.0-5.24 pican 0.6 walnut 0.3</p> <p>* For nuts: porsion 1 ½ ounce. <i>Source: Thaler ,1967 ; USDA (2002); Tokuşođlu,2007</i></p>	<p>SEAFOOD</p> <p>crab,frozen 5.9 herring 1.8 mackerel 1.6 trout 1.35</p> <p>MEAT</p> <p>beef liver 0.9-1.6 chicken meat 0.15-0.4 lard 0.6</p> <p>VEGETAB.</p> <p>peas 4.0-6.0 cabbage 2.0-3.0 beans 1.0-4.0 tomato 0.9 spinach 0.2-6.0 lettuce 0.2-0.8 carrot 0.2 onion 0.3</p> <p>EGG</p> <p>egg yolk 3.0 egg 0.5-1.5</p> <p>DAIRY</p> <p>milk 0.02-0.15 infantformula 8.93-27.72 cheese 0.4</p> <p><i>Source: Thaler,1967 ; Akalın & Tokuşođlu, 2004</i></p>

Vitamin E level in breast milk of Turkish mothers was 9.84 $\mu\text{g}/\text{ml}$ whereas 7.7 $\mu\text{g}/\text{ml}$ in a study in East-Jakarta and 9.7 $\mu\text{g}/\text{ml}$ in a study in Germany (31,34,35). China breast milk level of Vitamin E was reported as 6.98 $\mu\text{g}/100$ ml which is considered to be low when compared with those from Europe, USA, and Japan (36).

Good nourishment of the mothers can provide balanced composition of fat-soluble vitamins containing α -tocopherol in breast milk. The total lipid of breast milk is not strongly affected by the diet, but is related to maternal body composition (31,33). It was reported that there was not any statistically significant relation between vitamin E levels in mothers' milk and frequency of consumption of any type of food ($p>0.05$) (31). There was not any significant relation between as body mass index (BMI) of the mothers and that vitamin levels in their milk,either (31).

Plasma tocopherol levels vary with the total plasma lipid levels. and normally, the plasma α -tocopherol level is 5 to 20 $\mu\text{g}/\text{mL}$ (13).

Table 2.2.1.4. Dietary Reference Intake Values for Vitamin E by Life Stage Group							
Group	mg/day	RDA ^b		mg/day	IU RRR	UL ^c	
		IU RRR	IU all-rac			IU all-rac	
Adult	15	23	34	1000	1500	1100	
Pregnancy	15	23	34	1000	1500	1100	
Lactation	19	29	43	1000	1500	1100	

*For Adult= Criterion: Intakes sufficient to prevent hydrogen peroxide-induced hemolysis *in vivo*.
*For Pregnancy= Adult EAR
*For Lactation= Adult EAR plus average amount secreted in human milk
[EAR=(Estimated Average Requirement).The intake that meets the estimated nutrient needs of half the individuals in a group].
[RDA= (Recommended Dietary Allowance). The intake that meets the nutrient needs of almost all (97%--98%) of individuals in a group].
[UL= (Tolerable Upper Intake Level). The highest level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals].

Source: Adapted from Food and Nutrition Board, Institute of Medicine in *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, Carotenoids*, National Academy Press, Washington, 2000, p.186-283.

According to Panel on Dietary Antioxidants and Related Compounds, FNB Institute of Medicine at 2000, the dietary reference intakes (DRIs) for vitamin C, vitamin E, selenium, carotenoids were published (37). The 2000 RDA for adults (both men and women ≥ 19 years) defined as *2R*- α -tocopherol is 15 mg/day and defined as *all-rac* is 34 IU (TABLE 2.2.1.4.) (37). Increased intake of polyunsaturated fatty acids increases the need of vitamin E (2). Supplement pills containing vitamin E with natural stereochemistry (*RRR*- α -tocopherol) (*D*- α -T) and containing with synthetic (*all-rac*- α -tocopherol) (*DL*- α -T) are the most important source of vitamin E in USA diet (8).

Deficiency of Vitamin E

Dietary vitamin E deficiency is common in developing countries. Vitamin E deficiency causes degeneration of the axons of neurons (nerve cells) resulting in neurologic deficits, and fragility of red blood cells which is generally diagnosed as hemolytic anemia (13). Vitamin E deficiency may develop that genetic defects in the tocopherol transfer protein, genetic defects in lipoprotein synthesis or may develop as a result of fat malabsorption problems (8).

Retinis pigmentosa generally accompanies vitamin E deficiency in humans. It is shown that α -tocopherol supplementation (400 IU/day) with 15,000 IU/day of vitamin A stops or slows the retinis pigmentosa progression. Children with cystic fibrosis can become vitamin E deficient owing to the impaired secretion of pancreatic digestive enzyme causes steatorrhea and vitamin E malabsorption (8).

2.2.2. The Biochemistry, Functionality and Dietary Reference Intakes of Vitamin A and Carotenoids

Vitamin A:

Vitamin A-active compounds are represented by retinoids (as vitamin A) and the carotenoid precursors of vitamin A (provitamin A carotenoids) (52). Vitamin A is generic term for a group of closely related compounds also known as retinoids. In addition to its role as a chromophore in retina for vision, vitamin A is crucial micronutrient in human diet for reproduction, growth, cell metabolism, cell and tissue differentiation, haematopoiesis, bone development, pattern formation during embryogenesis and maintenance of the immune system (51,52,54,55,31).

The various retinoids (FIGURE 2.2.2.1) are present in animal tissues as a result of the enzymatic cleavage of ingested provitamin A carotenoids (52).

Dietary vitamin A is stored in the liver, normally, the liver stores 90% of the body's Vitamin A. To use Vitamin A, it is secreted into the bloodstream. The body releases it into the circulation bound to prealbumin (transthyretin) and retinol-binding protein (52,53,2).

The circulating retinol is taken up by target cells and oxidized in part to retinoic acid, that induces the protein synthesis via the direct control of gene expression. This gene activation establishes vitamin A (in the form of its metabolite, retinoic acid) as a hormone, similar to the steroid hormones and the thyroid hormone (52).

Vitamin A is important for reproduction of male and female. Retinol is required for normal spermatogenesis in the male whereas it is crucial for conception and normal fetus development in the female. Retinol is required for the formation of rhodopsin, a photoreceptor pigment in the retina. It is reported that vitamin A helps maintain epithelial tissues (52,2).

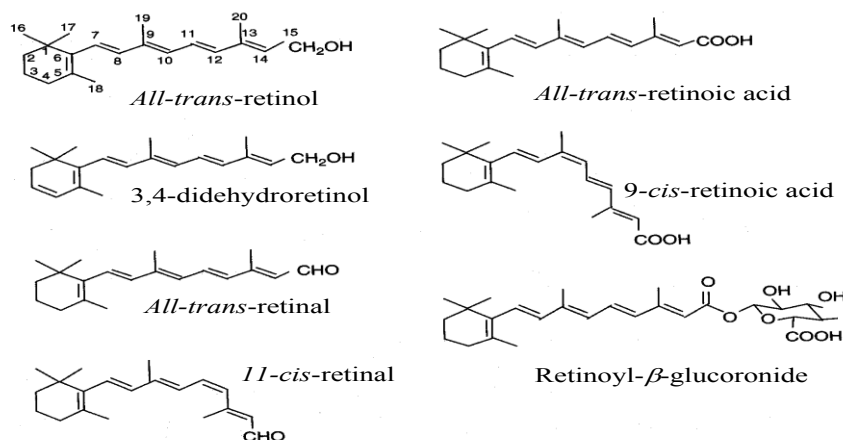


Figure 2.2.2.1. Retinoid family and major metabolites in foods. **Source:** Ross CA, Harrison EH. 2007. Vitamin A: Nutritional Aspects of Retinoids and Carotenoids. In *Handbook of Vitamins*. Zemleni J, Rucker RB, Mc Cormick DB, Suttie JW. 4th edition. p:1-39. CRC Press, Taylor & Francis Group, Boca Raton, FL

Retinol structure comprises a cyclohexenyl (β -ionone) ring attached at the carbon-6 (C-6) position to a polyene side chain whose four double bonds give rise to *cis-trans* (geometric) isomerism as shown in Figure 2.2.2.1. (51,52).

The *all-trans* form is the most active biologically and more stable than the other retinoids (53). Retinol (Figure 2.2.2.1) is most often present in tissues in esterified form, where the fatty acyl group is usually palmitate with lesser amounts of stearate and oleate esters. Esterification protects the hydroxyl group from oxidation. Retinyl esters are the major form of vitamin A in the body as a whole and the predominant form (more than 95%) in chylomicrons, cellular lipid droplets, and milk fat globules (52). The retinoids elicit the functions of vitamin A through their ability to regulate gene expression at specific target sites in the nucleus of cells (54,55). *All trans*-retinoic acid (Figure 2.2.2.1) is the most bioactive form of vitamin A. Retinoic acid is also the most potent natural ligand of the retinoid receptors, RAR and RXR. 9-*cis*-retinoic acid is capable of binding to the nuclear receptors may be a principal ligand of the RXR. 13-*cis*-retinoic acid is present in plasma, often at a level similar to *all-trans*-retinoic acid, and its therapeutic effects are well reported (51).

Carotenoids:

Carotenoids are yellow, orange, red, or violet pigments that are responsible for the color of many fruit and vegetables (56). Certain almost-colorless carotenoids also exist, such as phytofluene, that fluoresces intensely under ultraviolet (UV) irradiation. Carotenoids are synthesized by photosynthetic plants and some algae and bacteria, but not by animal tissues (Figure 2.2.2.2.).

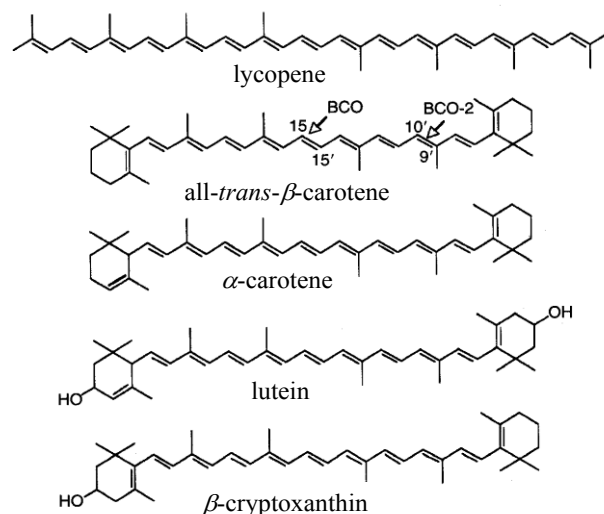


Figure 2.2.2.2. Major carotenoids in foods **Source:** Ross CA, Harrison EH. 2007. Vitamin A: Nutritional Aspects of Retinoids and Carotenoids. In *Handbook of Vitamins*. Zempleni J, Rucker RB, Mc Cormick DB, Suttie JW. 4th edition. p:1-39.

Carotenoids are classified as provitamins and can be considered chemically as derivatives of $C_{40}H_{56}$ polyene composed of eight isoprenoid units (Figure 2.2.2.2.). Derivatives are formed by a variety of reactions that include cyclization, hydrogenation, dehydrogenation and insertion of oxygen. In this context, carotenoids are classified as four groups as shown below (57).

- * Carotenoid Hydrocarbons
- * Carotenoid Alcohols(Xanthophylls)
- * Carotenoid Ketons
- * Carotenoid Acids

Hydrocarbon carotenoids are known as “*carotenes*”, and the oxygenated derivatives are termed “*xanthophylls*” (52,57)

carotene and other provitamin carotenoids, contained in green leafy and yellow vegetables and deep-or bright-colored fruits, are converted to Vitamin A. More than 600 carotenoids have been identified, but most nutrition research has focused on the several carotenoids: α -carotene, β -carotene, lycopene, lutein, zeaxanthine, β -cryptoxanthine, β -apo-8'-carotenal, β -apo-8'-carotenoic-acid and canthaxanthine (57). Carotenoids are absorbed better from vegetables when they are cooked or homogenized and served with some fats or oils (58).

Beta-carotene occurs widely in plant products and has a high vitamin A activity. One molecule of β -carotene, could yield two molecules of vitamin A (FIGURE 2.2.2.2.). After cleaving of β -carotene, the first reaction product is retinal, that is reduced to retinol. To have vitamin A activity, the carotenoid molecule must incorporate a molecule of retinol, i.e., an unsubstituted β -ionone ring with an 11-C polyene chain. β -carotene ($C_{40}H_{56}$), the most ubiquitous provitamin A carotenoid, is composed of two molecules of retinol joined tail to

tail; therefore the compound has maximal (100%) vitamin A activity. The chemical structures of all other provitamin A carotenoids incorporate one molecule of retinol and thus theoretically contribute 50% of the biological activity of β -carotene (2,51).

Lycopene (FIGURE 2.2.2.2.) is an acyclic carotenoid with 11 linearly arranged conjugated double bonds, which is found only in few foods. Tomatoes and tomato products are the main foodstuffs contributing the dietary intake of lycopene. In addition, apricots, guavas, watermelons, papayas, pink grapefruits, rosehips contain lycopene (59-61). Due to the lacking the β -ionone ring structure, lycopene does not have any provitamin A activity. Lycopene is an efficient antioxidant and singlet oxygen quencher. Recent epidemiological researches reported that lycopene has preventive agent for cardiovascular diseases and cancer (59-61).

Lutein (Figure 8.2.2.3.) and its stereo isomer zeaxanthin (Figure 2.2.2.4.) are members of the xanthophyll family of carotenoids. The xanthophylls lutein and zeaxanthin have attracted a lot of interest due to the it was presumed that both compounds may prevent adult macula degeneration (AMD), age-related cataract information (38-41) and may delay chronic disease (39-40) and some forms of cancer (42).

As antioxidants, lutein and zeaxanthin can also inhibit the formation of damaging free radicals by quenching singlet oxygen. Conjugated double bonds are highly effective in quenching singlet oxygen; therefore, the fact that zeaxanthin has an extra conjugated double bond may take it a better antioxidant than lutein (43,50) (Figure 2.2.2.5).

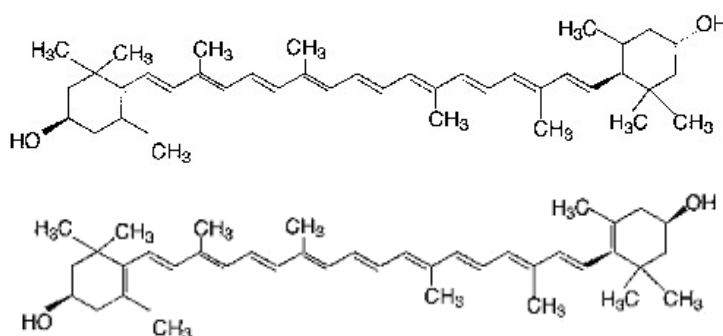


Figure 2.2.2.4. Zeaxanthine

Moreover dark-green leafy vegetables (especially spinach, kale, collard, broccoli, mustard), corn, orange peppers, orange, kiwi, tangerine and various kinds of squash (44,45); egg yolks also serve as traditional source of xanthophylls (46,47). Especially lutein and zeaxanthin in yolks might be highly bioavailable because of their association with the lipid matrix of the egg yolk (46,50) (Figure 2.2.2.5)

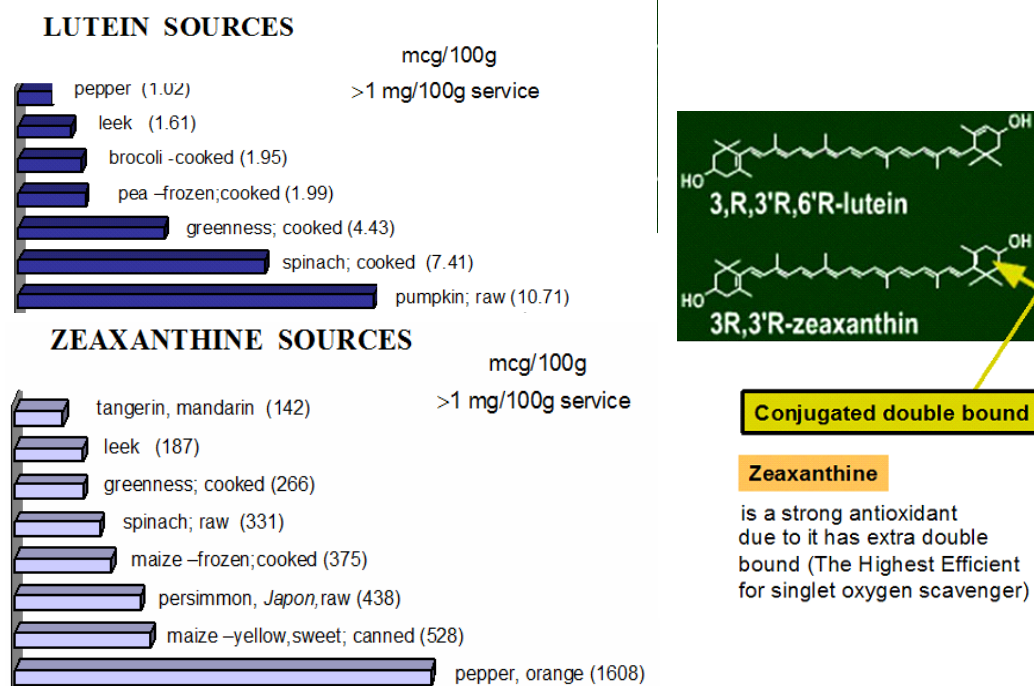


Figure 2.2.2.5. Lutein and zeaxanthine levels in foods (57,62)

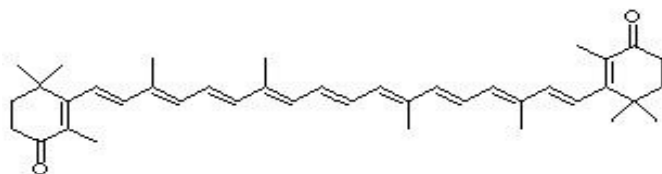


Figure 8.2.2.6. Canthaxanthine

It has been observed that canthaxanthin (Figure 2.2.2.6.) has antioxidant capabilities *in vitro*. It is showed that canthaxanthin was able to reduce UV-light induced tumours (48,49).

In medium egg yolks that have 61.04 g of average total weight and 17.84 g of yolk weight; lutein as 844.57 $\mu\text{g}/\text{yolk}$ (avg.), zexanthine, as 12.95 $\mu\text{g}/\text{yolk}$ (avg.) and canthaxanthine as 11.4 $\mu\text{g}/\text{yolk}$ (avg.) were determined, based on dry weight ($p < 0.01$) (50). It has been put forwarded that a standardization should be necessary regarding in enhanced functional egg (enhanced nutraceutical egg) with xanthopyll carotenoids (50). In the same research, afterwards the heating process, it is also reported that lutein decreased as 21.43% in soft-boiled yolk and as 38.22% in hard-cooking yolk whereas zexanthine reduced as 1.88% in soft-boiled, as 32.53% in hard-cooking yolk and canthaxanthine decreased as 6.99% in soft-boiled yolk and as 45.80% ($p < 0.01$) (50).

Dietary Value of Vitamin A

The vitamin A value of foods has traditionally been expressed in International units (IU). One IU is defined as the amount of vitamin A activity contained in 0.334 μg of *all-trans*-retinyl acetate, that is equivalent to 0.300 μg of *all-trans*-retinol (52).

$$\text{RE} = \mu\text{g retinol} + \frac{\mu\text{g } \beta\text{-carotene}}{6} + \frac{\mu\text{g other provitamins}}{12}$$

It is reported that the IU values can be converted to retinol equivalents. The convert IU into RE on the basis of retinol, 1 RE = 1 μg retinol and 1 IU = 0.3 μg retinol. Therefore; 1 RE = 1/0.3 = 3.33 IU vitamin A activity from retinol (52). In the RE system, 1 μg retinol = 6 μg β -carotene, whereas in the IU system, 1 μg retinol = 2 μg β -carotene. It is reported that, the conversion of IU to RE on the basis of β -carotene, one must first multiply the IU by a factor of 3 (6/2), to make the equivalency the same as that of the RE system, and then multiply by 3.33 (52).

In 2001, the U.S. Institute of Medicine recommended the replacing the RE with the retinol activity equivalent (RAE) and the redefining the average equivalency values for carotenoids in foods in comparison with retinol (53). 1 μg RAE is defined as 1 μg of *all-trans*-retinol, and thus is the same as 1 μg RE. Both are equal to 3.3 IU of retinol. The equivalency of provitamin A carotenoids and retinol in the RAE system as shown below. RAE terminology is not yet fully utilized, the vitamin A values in some food tables, food labels, and supplements are still expressed in RE or IU.

Figure 2.2.2.7. shows digestion and absorption mechanism of antioxidants. This describes the path of a general antioxidant compound from the food matrix through the human body (41). For a food component to be absorbed, it must be released from the matrix and be accessible to the brush-border of the small-intestine in a form that it can be absorbed by the enterocyte either by passive diffusion or by an active transporting system (41). That process is time-dependent. It depends upon an array of variables containing: (I) the state of food (raw, cooked and/or processed), (II) the presence and efficiency of digestive enzymes and other endogenous digestants, (II) the composition of meal (41). For carotenoids, food processing is important facilitator for carotenoid bio-accessibility. The availability for absorption is enhanced by, for instance, the carotenoid transfer to the lipid phase during cooking in the presence of oil, and by disruption of the cellular matrix during mastication (41). Vitamin E, carotenoids and other lipid soluble components are absorbed via the mucosa of small intestine, mainly in duodenum (63,64). The carotenoids are transported through the enterocyte from the luminal to the serosal side. These carotenoids are incorporated into lipoproteins, that are then released into the systemic circulation (41, 65) (FIGURE 2.2.2.7.).

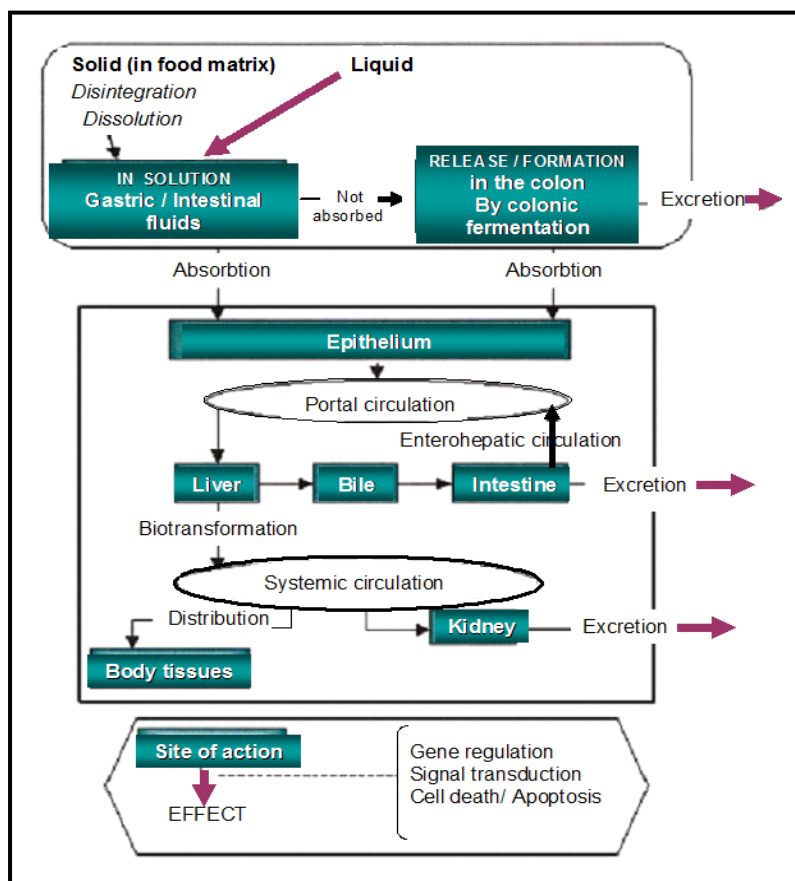


Figure 2.2.2.7. Digestion and absorption of antioxidants. **Source:** Alves-Rodrigues A, Shao Andrew 2004. *The Science Behind Lutein. Toxicology Letters.* 150, 57-83.

Table 2.2.2.1. Vitamin A and carotene levels of some foods***Source:** de Man,1999 ; USDA,2004; Demirci,2003

FOOD	Vitamin A (IU/100g)	Carotene (mg/100g)
Animal Sources		
Beef liver	6000-14000	-
Calf's liver (4 oz-wt)	30485	-
Butter (May-Nov.)	2363-3452	0.43-0.77
Cheddar cheese	553-1078	0.07-0.71
Milk	110-307	0.01-0.06
Egg yolk (raw)	1000-4000	-
Egg (boiled)	165-488	0.01-0.15
Herring (canned)	178	0.07
Sole	450	-
Beef (grilled sirloin)	37	0.04
Vegetables & Fruits (1 cup)		
Carrots, raw	34317	-
Spinach (boiled)	14742	6.0
Sweet potato, baked, with skin	13107	-
Turnip greens (cooked)	7917	-
Kale (boiled)	9620	-
Cantaloupe, cubes	5158	-
Winter squash, baked, cubes	7292	-
Mustard greens (boiled)	4243	-
Collard greens (boiled)	-	-
Bell peppers (red, raw, slices)	5244	-
Tomato (ripe)	1121	-
Tomato (canned)	-	0.5
Asparagus (boiled)	970	-
Apricot (1 each)	914	-
Papaya(1 each)	863	-
Broccoli (steamed)	2281	2.5
Peach	-	0.34
Cabbage (shredded,boiled)	198	0.3

Table 2.2.2.1.shows vitamin A and carotene content of some foods whereas TABLE 2.2.2.2. indicate vitamin A levels of some fortified foods.

Table 2.2.2.2. Vitamin A levels of some fortified foods*

Fortified Foods	Vitamin A (mg/100g)
Margarines	~0.8
Powdered breakfast drinks	3-6
Ready-to- eat cereals	0.7-1.5

Calf liver is an excellent source of preformed vitamin A. Cow's milk and eggs are good sources of preformed vitamin A. NHANES data 2001-2002 for food consumption in the USA showed that the major contributors to the intake of preformed vitamin A are milk, margarine, eggs, beef, liver, ready-to-eat cereals, whereas the excellent sources of provitamin A carotenoids are carrots, sweet potatoes, cantaloupes and spinach (69).

As a vitamin supplement, vitamin A is available as retinol and retinyl-palmitate. Retinoic acid is the form of vitamin A found in medications prescribed for the treatment of skin disorders (68).

Table 2.2.2.3. shows the dietary reference intake values for vitamin A by life stage group according to the Institute of Medicine at 2002 (53). The dietary reference intakes (DRIs) established by the Institute of Medicine (IOM) are a set of reference values including the estimated average requirement (EAR), recommended dietary allowance (RDA), adequate intake (AI), and tolerable upper intake level (UL).

During pregnancy, the intake and hepatic reserves of maternal vitamin A are essential to guarantee the transference of this micronutrient to the foetus, and its first source of the nutrient. The observed average vitamin A intake of women in developing countries (660 μg retinol equivalents/day) is less than one-half of the amount taken in developed countries (1,540 μg retinol equivalents/day) (54,55). Adequate amounts of vitamin A cross the placenta to the foetus, especially in the last trimester; however, vitamin A stores in the newborn liver are relatively low compared with those of older infants and children (54,55).

Table 2.2.2.3. Dietary Reference Intake Values for Vitamin A by Life Stage Group

Group	RDA ($\mu\text{g}/\text{day}$) ^a	UL ($\mu\text{g}/\text{day}$) ^b
■ Infants		
0-12 months	400 ^c	600
■ Children		
1-3 years	300	600
4-8 years	400	900
■ Adolescent and adult males		
9-13 years	600	1700
14-18 years	900	2800
19 to \geq 70 years	900	3000
■ Adolescent and adult females		
9-13 years	600	1700
14-18 years	700	2800
19 to \geq 70 years	700	3000
■ Pregnancy		
<18 years	750	2800
19-50 years	770	3000
■ Lactation		
<18 years	1200	2800
19-50 years	1300	3000

^aAs retinol activity equivalents (RAEs)
^bAs μg preformed vitamin A (retinol)
^cAdequate intake (RAEs)

Source: Food and Nutrition Board, Institute of Medicine in *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*, National Academy Press, Washington, 2002, p.8-9.

Human breast milk is an excellent source of vitamin A. The vitamin A content of human milk is more influenced by maternal dietary intake than by mother's vitamin A status. The sources of vitamin A for milk synthesis are plasma retinol-binding protein (RBP)-retinol and retinyl esters in chylomicrons. The former source is relatively constant after the initial decrease regardless of vitamin A status (liver stores), where the latter is directly related to the maternal intake (54,55)*.

Table 2.2.2.4. Retinol concentration in breast milk and plasma.

Retinol concentration*	Total milk (n=46)	İzmir group (n=26)	Manisa group (n=20)
Plasma ($\mu\text{mol/l}$)			
Average	126.0 \pm 36.0	123.0 \pm 17.0	129.0 \pm 23.0
Minimum	70.0 \pm 12.56	70.0 \pm 12.56	74.0 \pm 13.64
Maximum	212.0 \pm 30.7	184.0 \pm 21.5	212.0 \pm 30.7
Milk ($\mu\text{g}/100\text{ml}$)			
Average	82.47 \pm 17.0	81.0 \pm 10.1	84.0 \pm 9.02
Minimum	56.83 \pm 8.84	57.92 \pm 6.92	56.83 \pm 8.84
Maximum	113.8 \pm 23.2	112.83 \pm 16.76	113.8 \pm 23.2

*($p < 0.05$)
Source: Adapted from by Tokuşoğlu *et al.* 2008. *Int.J.Food Sci.Nutr.*59(2), 166-174
 Retinol and alpha-tocopherol concentrations in breast milk of Turkish lactating mothers under various socio-economic status

Table 2.2.2.4. shows that retinol concentration in breast milk and plasma of lactating mothers living in two different area of Turkey (31). If the plasma retinol concentration is less than 20.05 $\mu\text{g}/100\text{ ml}$ over 15% of a specific population, vitamin A deficiency is defined to be of public health importance. It was reported that none of the mothers in whom plasma vitamin A levels were found had a value less than 20.5 $\mu\text{g}/100\text{ ml}$ and vitamin A concentrations of both plasma and breast milk were appropriate scale for investigated lactating womans in above-mentioned study (Table 2.2.2.4.) (31).

A retinol level in breast milk less than 30.09 $\mu\text{g}/100\text{ ml}$ is considered to be consistent with vitamin A deficiency in lactating women. Prevalance rates of <10%, $\geq 10\%$ to <25%, and $\geq 25\%$ of breast milk retinol <30.09 $\mu\text{g}/100\text{ml}$ are considered to indicate mild, moderate, and severe vitamin A deficiency, respectively, as a public health problem based on WHO (70).

Dietary deficiency of vitamin A is quite common in developing countries, and is associated with the high incidence of blindness, viral infections and child mortality which occurs in impoverished populations (53). Vitamin A deficiency is a primary cause of xerophthalmia, that is manifested as night blindness and corneal abnormalities leading to irreversible blindness. Enough vitamin A level is absorbed and stored quickly, and released and used slowly, to prevent the development of xerophthalmia over an extended period (8,71).

It is estimated that vitamin A administered at doses of 200,000 IU (60 mg retinol) every 6 months would reduce total mortality by 35% in preschool children (72).

Vitamin A reduced measles-related morbidity and mortality (8, 73). Owing to the protective role of vitamin A, WHO/UNICEF recommended in 1987 that in those countries where the measles fatality rate is 1% or greater, all the children diagnosed with measles should receive 30-60 mg of vitamin A immediately (8,74). The American Academy of Pediatrics has also recommended vitamin A in the treatment of high-risk children with measles (75).

Vitamin A deficiency also affects the skin health, the health of hair, eyes, and immune system, though loss of appetite, bone abnormalities. A tell-tale sign of vitamin A deficiency is hyperkeratosis, a goose bump-like appearance of the skin caused by excessive production of keratin (a protein found in skin) that blocks hair follicles. Growth retardation are also associated with inadequate intake of vitamin A (53).

Vitamin A can cause side effects when taken in excessive amounts. High storage amounts of vitamin A in the body (hypervitaminosis A) that can lead to toxic symptoms. Most causes of vitamin A toxicity are due to accidental ingestion of doses exceeding 660,000 IU (200 mg of retinol equivalents) and 330,000 IU (100 mg of retinol equivalents) by adults and children, respectively (53). Signs of vitamin A toxicity include nausea, loss of appetite, vomiting, headache, irritability, dizziness, blurred vision, lack of muscular coordination, abnormal liver functions, pain in weight-bearing bones.

2.2.3. The Biochemistry, Functionality and Dietary Reference Intakes of Vitamin D

Vitamin D is represented by cholecalciferol (vitamin D₃) and ergocalciferol (vitamin D₂), that are structurally similar secosteroids derived from th UV irradiation. The generic term vitamin D designates a group of chemically related compounds which possess antirachitic activity. Members of D-family are derived from the cyclopentanoperhydrophenantrene ring system as shown in FIGURE 2.2.3.1. (52,112).

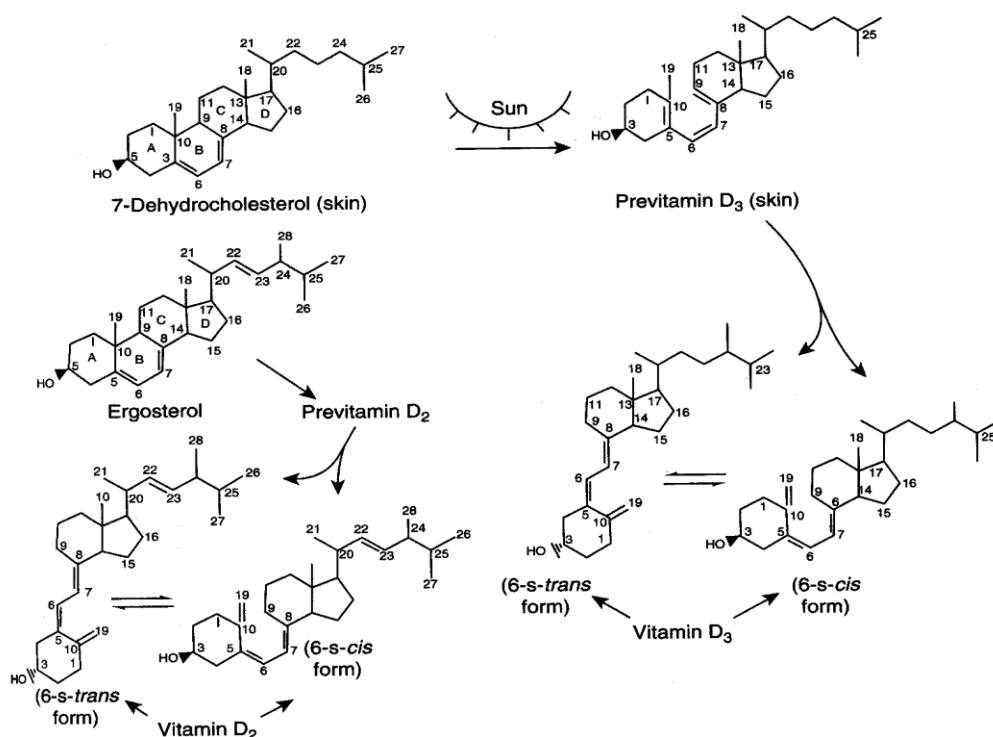


Figure 2.2.3.1. The chemistry and irradiation pathway for production of vitamin D₃ and vitamin D₂.

It is shown that provitamins D were converted to vitamin D on treatment with UV radiation (Figure 2.2.3.1). The primary structural requirement for a provitamin D is a sterol with C-5 to C-7 diene system in ring B (112). It is determined that the conjugated double-bond system is a chromophore, which on UV irradiation initiates a series of transformations resulting in the production of the vitamin D secosteroid structure (Figure 2.2.3.1) (112).

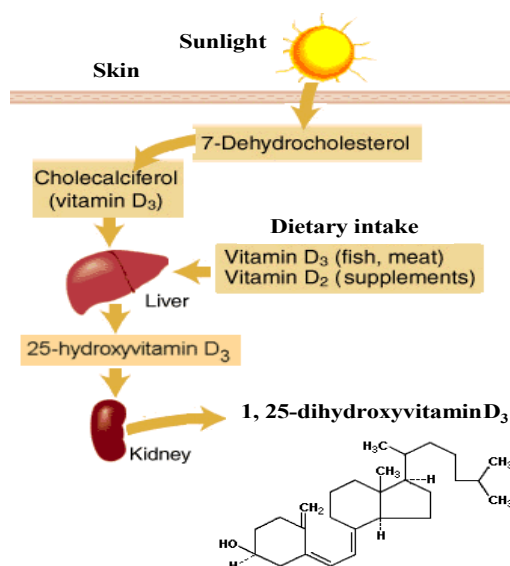


Figure 2.2.3.2. The metabolic pathway for production of 1,25-dihydroxyvitamin D₃ from kidney.

Vitamin D₃ that is described as 1,25-dihydroxyvitamin D₃ is synthesized in skin by exposure to sunlight (ultraviolet radiation). Vitamin D₃ is metabolized by the liver to 25(OH)D, which is then converted by the kidneys to 1,25(OH)₂D (1,25-dihydroxycholecalciferol, calcitriol, or active vitamin D hormone). 25(OH)D, the major circulating form, has some metabolic activity, but 1,25(OH)₂D is the most metabolically active (FIGURE 2.2.3.2).

Vitamin D intake has been hypothesized to reduce the risk of several types of cancer. Vitamin D and its analogues have demonstrated anticancer activity *in vitro* and in animal models (76).

However, the risk of colorectal cancer in relation to dietary vitamin D remains controversial (76). Studies that combine multiple sources of vitamin D or examine serum 25(OH)D₃ usually find that above-average vitamin D intake and serum metabolite concentrations are associated with significantly reduced incidence of colorectal cancer (76).

1,25-dihydroxyvitamin D₃ obtained in the diet chiefly in fish liver oils and egg yolks. In some developed countries, milk and other foods are fortified with vitamin D.

In vitro and animal studies indicate that vitamin D may have anti-cancer benefits, including against progression and metastasis, against a wide spectrum of cancers (77). It was reported that supporting an anti-cancer effect of vitamin D is the ability of many cells to convert 25(OH)D, the primary circulating form of vitamin D, into 1,25(OH)₂D, the most active form of this vitamin (77). It was declared that higher 25(OH)D levels through increased sunlight exposure or dietary or supplement intake inhibit colorectal carcinogenesis is substantial. The suppression of circulating 1,25(OH)₂D levels by calcium intake could explain why higher calcium and milk intakes appear to increase risk of advanced prostate cancer (77).

The association of specific circulating 25(OH)D concentrations with bone health outcomes in children, women of reproductive age, postmenopausal women and elderly men; the effect of dietary intakes (foods fortified with vitamin D and/or vitamin D supplementation) and sun exposure on serum 25(OH)D; the effect of vitamin D on bone mineral density (BMD) and fracture or fall risk; and the identification of potential harms of vitamin D current reference intakes (78). It was reported that intakes from vitamin D-fortified foods (11 randomized controlled trials RCTs) consistently increased serum 25(OH)D in both young and older adults. It is also shown that vitamin D₃ in combination with calcium results in small increases in BMD compared to placebo in older adults although quantitative synthesis was limited due to variable treatment durations and BMD sites (78).

In humans, patients with hypocalcemic vitamin D-resistant rickets type II have high circulating vitamin D levels and vitamin D resistance due to expression of a dysfunctional vitamin D receptor (VDR) (79).

One of the major functions of vitamin D is maintaining proper calcium and phosphorous levels in the blood. The simply description of the most metabolically active form of vitamin D (1,25-dihydroxy-cholecalciferol) is "Calcitriol" (80). Calcitriol works with parathyroid hormone (PTH) to maintain proper levels of calcium in the blood. Low levels of calcium in the blood stimulate the secretion of PTH from the parathyroid gland. when blood levels of calcium are too high, calcitriol decreases the intestinal absorption of calcium and stimulates the bones to take up calcium, thereby decreasing blood calcium levels. Without adequate phosphorus, bone cannot be properly mineralized, which contributes to the defects seen in osteomalacia. In addition, the new bone cells being laid down by the osteoblasts (the cells that create new bone) absorb more water and swell, causing the bone pain associated with osteomalacia (80).

Vitamin D may play an important role in regulating cellular growth and function in human brain cells. In mice studies, vitamin D has been found to have a significant effect on brain cell (neuronal) growth and division (80). Vitamin D also helps regulate immune system activity, preventing an excessive or prolonged inflammatory response. Immune cells of humans, specifically active T-cells, have receptors for vitamin D. For example, in multiple sclerosis, T helper cells drive the progression of the disease by recruiting other inflammatory immune cells (macrophages and inflammatory cytokines)-particularly when vitamin D is deficient. When vitamin D levels are adequate, the body switches on a vitamin-D mediated system that can help shut down the inflammation. Vitamin D's anti-inflammatory effects are seen across a wide spectrum of health conditions including hypertension, type 1 diabetes, and psoriasis (80).

One possible mechanism involves the relationship between vitamin D and renin levels, since renin, an enzyme secreted by the kidney, is important in regulation of blood pressure and heart health (80). Vitamin D deficiency accelerates progression to type 1 diabetes in diabetic-prone mice, but if they are given Vitamin D₃, their risk of progression decreases by 80%. Whether this relationship holds true for humans has yet to be determined (80).

Table 2.2.3.1. shows vitamin D levels of some foods (Table 2.2.3.1.). As shown the data from Table 2.2.3.1., vitamin D that occurs naturally in unfortified foods is generally derived from animal products. Salt-water fish such as herring, salmon, sardines contain substantial amounts of vitamin D and cod fish-liver oils are extremely rich sources. (81,112). Eggs (egg yolk), beef, unfortified milk, butter supply only small amounts of vitamin D. Another food sources such as fruits and vegetables have no contain vitamin D. Therefore dietary requirements for vitamin D can only met by the fortification of suitable foods, containing margarine, butter, fresh and evaporated milk, cereals and chocolate mix (112).

Table 2.2.3.1. Vitamin d levels of some foods*

FOOD	Vitamin D ($\mu\text{g}/1000\text{g}$)	Vitamin D (IU)
Animal Sources		
Liver (beef,pork)	2-5	-
Liver, beef,cooked, 3 ^{1/2} ounces	-	15
Eggs	44	-
Eggs (1 whole) [■]	-	20
Fats & Dairy		
Margarine, fortified 1 tablespoon		60
Butter	2-40	-
Milk	0.9	-
Cow's milk, 2% (1 cup)	-	98
Cheese	12-47	-
Cheese (Swiss, 1 ounce)	-	12
Pudding (with vit.D fortified milk)	-	50
Seafood		
Herring oil	2,500	-
Cod liver oil, 1 tablespoon	-	1360
Salmon (chinook,baked/broiled) *	-	411
Mackerel, cooked 3 ^{1/2} ounces	-	345
Salmon, cooked 3 ^{1/2} ounces	-	360
Sardines (canned,in oil) 1 ^{3/4} ounces	-	250
Tuna fish (canned,in oil) 3 ounces	-	200
Shrimp (steamed/boiled) *	-	162
Cod (baked/broiled) *	-	64

* 4 oz-wt; [■] vit.D. is found in egg yolk.

Source: de Man,1999 ; USDA,2004;2003

Dietary Value of Vitamin D

One IU of vitamin D is the activity of 0.025 μg of crystalline cholecalciferol. An expert committee in 1970 recommended that the intake of vitamin D be expressed as μg of cholecalciferol rather than as IU (52).

The World Health Organization has defined the International unit (IU) of vitamin D₃ as “the vitamin D activity of 0.025 μg of the international standard preparation of crystalline vitamin D₃.”

By USA Food and Nutrition Board of the Institute of Medicine in current adequate intake allowance of vitamin D is 200 IU/day (5 $\mu\text{g}/\text{day}$) for all life stage group (82).

As shown in Table 2.2.3.2., for males and females ages 51-70 or more than 70, the adequate indicated level is set at 400 IU/day (10 $\mu\text{g}/\text{day}$) or 600 IU/day (15 $\mu\text{g}/\text{day}$) (82).

Table 2.2.3.2. Dietary Reference Intake Values for Vitamin D₃ by Life Stage Group

Group	RDA (IU/day)	$\mu\text{g}/\text{day}$
■ Infants	200	5
■ Children	200	5
■ Adult males	200	5
■ Adult females (18-51 years)		
Pregnancy	200	5
Lactation	200	5
■ Adult males (51 to ≥ 70 years)	400 (600)	10 (15)
■ Adult females (51 to ≥ 70 years)	400 (600)	10 (15)

^bAs μg vitamin D₃.,
Source: FNB (1997)

It is demonstrated that the influence of season and latitude on the cutaneous photochemical synthesis of vitamin D₃ (83). The maximum vitamin D₃ production occurs in summer months and the production of D₃ photochemically through exposure to sunlight is significantly higher at latitudes close to the equator and falls off significantly at higher latitudes. The little or no vitamin D₃ may be generated in winter months (83,84). It is reported that there is a serious nutritional vitamin D₃ problem for Finland (e.g.,Helsinki), Alaska (e.g.,Fairbanks) or Canada (e.g.,Edmonton) peoples due to the latitudes higher than 50° with clear atmospheric conditions. No cutaneous production of this vitamin occurs during some periods of year (85).

Dietary deficiency of vitamin D results in insufficient intestinal absorption and renal reabsorption of calcium and phosphate. The serum calcium and phosphate levels decrease whereas serum alkaline phosphatase

activity increases. Qwing to the low serum calcium levels (5-7 mg/100 ml), hyperparathyroidism occurs (86). When parathyroid hormone (PTH) increases, along with vitamin D₃ deficiency, the bone demineralization develop. This situation result in rickets in children and osteomalacia in adults (86).

2.2.4. Utilization Strategies of Fortified Vitamin A,D,E

The level of fat soluble vitamins as A,D,E in fortified vegetable oils and margarine depends on consumption patterns and nutritional requirements. Clearly, prior to determining the level of nutrient to add to oils and fats, the use of and consumption patterns for margarine by different socioeconomic and age groups need to be determined in order to ensure that the maximum safe level of intake for each nutrient is not exceeded. Vegetable oils are suitable as vehicles for vitamins A,D,E fortification, as the production and refining of the oils is a centralized process. Vegetable oils are consumed by almost everyone; thus it is possible to improve people's access to fat soluble vitamins through fortification. Vitamin A,D,E are fat soluble, they can be uniformly distributed in oils. The stability of vitamin A is greater in oils than in any other foods and oil facilitates the absorption of vitamin A by the body.

Vitamin E, as tocopherol acetate, is added to fats and oils including margarine and fat spreads and breakfast cereals. The intake of vitamin E is known to be related to the total dietary intake of fat and it has been shown to enhance absorption and bio-conversion of dietary carotenoids to vitamin A. Emerging evidence indicates that daily intake of vitamin E greater than 30 IU may afford protection against the development of degenerative diseases. Optimal levels of fortification of vitamin E should be reassessed based on such scientific evidence. It is shown that fortifying margarine with vitamins A, D and E does not alter its flavor, making it an excellent carrier for these micronutrients. Foods made with fortified soybean oil including mayonnaise, fried beans, cooked rice, fried potatoes, soup, wheat tortillas, and fried meat showed excellent acceptability among consumers, who were not able to distinguish between products prepared with vitamin A fortified and unfortified oils. Studies in humans have shown that the bioavailability of vitamin A in cooked foods made with fortified soybean oil, is good.

Many important advantages exist for the edible oil as a medium for vitamin E fortification: Vitamin E completely soluble in oil and is uniformly distributed, vegetable oils consumed by all populations, absorption and utilization of vitamin E are better when consumed with fats and oils, fortification technology is simple and available, cost of fortification is relatively low and affordable for all income groups. Cost of fortification includes capital costs, such as blending equipment (tanks, propellers or agitators) and recurrent costs containing those for the premix, personnel, monitoring and evaluation. The production and fortification of margarine is carried out in a batch or continuous process. To ensure that the vitamins are uniformly distributed, mixing takes place in vertical tanks that contain turbines or propeller agitators. The vitamin A and D₃ blend mixed with warm oil in a ratio of 1:5 until a uniform solution is obtained. This premix is then incorporated into the margarine before the emulsifying process. β -karoten is also added to margarine (15-20 g/ton) of a 30% oily suspension) before the emulsifying step to enhance to color as well as to contribute to the vit A content the product.(FIG.2.2.4.1).

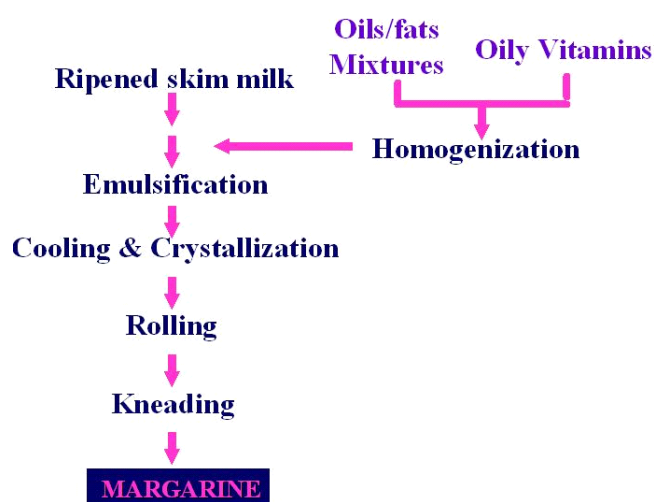


Figure 2.2.4.1. Flow chart of fortified margarine manufacturing. (source: adopted from tokusoglu, 2006. *Fortification Criteria of Vegetable Oils and Margarines with Alpha-Tocopherol and Tocopheryl Acetate: The Regulations on Vitamin E Labeling*. Lecture. In World Conference and Exhibition on Oilseed and Vegetable Oil Utilization, Processing, By-Products, Biodiesel, Specialty and Functional Oils, and New Applications & Technologies 14-16 August 2006, Istanbul)

2.2.5. The Biochemistry, Functionality and Dietary Reference Intakes of Folic Acid

Folic acid consist of a large group of related compounds having the same basic chemical structure as folacin, or pteroylglutamic acid (PteGlu), as differing in the state of reduction and the number of glutamate residues (FIGURE 2.2.5.1) (2,87,88).

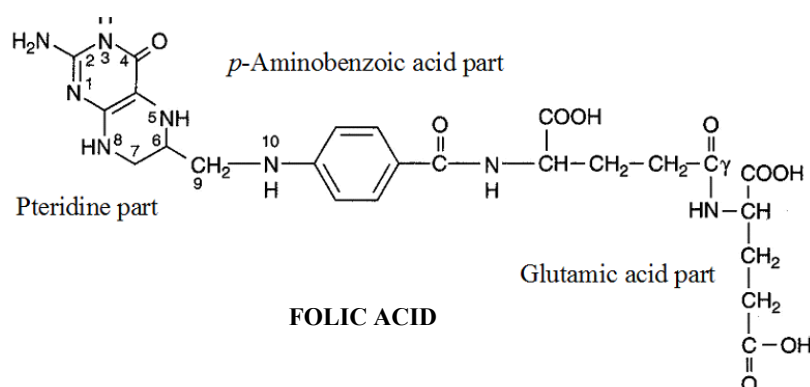


Figure 2.2.5.1. Folic Acid Basic Structure (88). **Source:** Adopted from Bailey LB. 2007. Folic Acid. In *Handbook of Vitamins*. Zemleni J, Rucker RB, Mc Cormick DB, Suttie JW.4th ed. p:153-174.CRC Press , Taylor & Francis Group, Boca Raton, FL.

Folate molecule, tetrahydrofolate (THF), also called vitamin B₉, is derived from 5,6,7,8-tetrahydropteroylglutamate, that consist of a 2-amino-4-hydroxy-pteridine (pterin) moiety linked via a methylene group at the C-6 position to a *p*-aminobenzoylglutamic acid (*p*ABG) (88) (FIGURE 2.2.5.1.).

Specific one carbon (C) units which can be added at N-5 or N-10 or both N-5 and N-10 positions of the polyglutamyl form of the THF molecule include methyl (CH₃), methylene (-CH₂-), methylenyl (-CH=), formyl (-CH=O), formimino (-CH=NH) groups. The pyrazine ring in THF is fully reduced at the 5,6,7,8 positions and the reduction at 7 and 8 positions yields dihydro folate (88).

Through the addition of glutamate residues by γ -peptide linkage, glutamic acid in the monoglutamate form of this vitamin can be converted to a glutamate chain (88).

Folic acid is involved in maturation of red blood cells and folacin deficiency produces a megaloblastic anemia. From 1940s to now, the therapeutic use of folic acid for the treatment of megaloblastic anemia is continuing. Since the Early 1990s, the links between folate intake and birth outcome or chronic disease risk were explored (88,94).

Biochemically, folic acid functions *in vivo* as coenzymes and carriers of one-carbon units for a number of enzyme reactions, containing amino acid synthesis, protein and nucleic acid synthesis which are required for development of the fetal nervous system. Folic acid participates in both anabolic and catabolic reactions (89,94).

It has been recently implicated that folic acid has crucial effects in a number of non-vitamin functions including roles in various types of cancer, coronary heart diseases, the prevention of birth defects such as neural tube abnormalities which are known neural tube defects (NTDs) (89-93). Adequate folic acid intake prior to conception and throughout the first trimester of pregnancy helps prevent certain brain and spinal cord defects such as spina bifida (94).

Folic acid is more readily available than the naturally occurring food folates but may be less available from fortified foods than in aqueous solution or tablet form. Food folates have been reported to be 30-80% as available as folic acid. Folic acid is absorbed in the duodenum and upper jejunum (87,89,95).

The bioavailability of folate may be defined as the portion of nutrient and influenced by various factors containing but not limited to the following: (a) chemical form of folate, (b) food matrix, (c) the chemical environment in the intestinal tract, (d) factors affecting the metabolic fate postabsorption (96).

Liver, especially beef liver is good source of folate. Folic acid is also naturally found in dried peas, dried beans such as black beans and kidney beans, germ, leafy and dark green vegetables such as spinach, lettuce, broccoli, fruits and fruit juices such as orange juice, tomato juice and also peanuts (81) (Table 2.2.5.1.).

In addition to food folate, ready-to-eat breakfast cereals contribute significantly to folate intake in the USA due to the majority of breakfast cereals in the United States marketplace contain about 100 μ g per serving of folic acid (97).

Folic acid is an added ingredient in a various food products containing meal replacement and infant formulas, and ready-to-eat cereals, snack bars and cereal grain products (such as bread, pasta, flour, rice) (98). Table 2.2.5.2. shows the folic acid levels of some folic acid fortified foods in United States (81) (Table 2.2.5.2.).

Table 2.2.5.1. Folate levels of some foods*

FOOD	Folate Content ($\mu\text{g}/100\text{g}$)
Liver	
Beef liver, cooked, braised, 3 ounces	185
Vegetables	
Cowpeas (blackeyes), immature, cooked, boiled, ½ cup	105
Spinach, frozen, cooked, boiled, ½ cup	100
Spinach, raw, 1 cup	60
Great Northern beans, boiled, ½ cup	90
Asparagus, boiled, 4 spears	85
Vegetarian baked beans, canned, 1 cup	60
Green peas, frozen, boiled, ½ cup	50
Broccoli, chopped, frozen, cooked, ½ cup	50
Broccoli, raw, 2 spears (each 5 inches long)	50
Lettuce, Romaine, shredded, ½ cup	40
Turnip greens, frozen, cooked, boiled, ½ cup	30
Germ	
Wheat germ, crude, 2 Tablespoons	40
Fruits	
Avocado, raw, all varieties, sliced, ½ cup sliced	45
Orange, all commercial varieties, fresh, 1 small	30
Cantaloupe, raw, ¼ medium	25
Papaya, raw, ½ cup cubes	25
Banana, raw, 1 medium	20
Fruit Juices	
Orange juice, chilled, includes concentrate, ¾ cup	35
Tomato Juice, canned, 6 ounces	35
Nuts	
Peanuts, all types, dry roasted, 1 ounce	40
Egg	
Egg, whole, raw, fresh, 1 large	25

Source: USDA,2003

Table 8.2.5.2. Folic acid levels of some folic acid fortified foods* source: usda,2003

FOLIC ACID FORTIFIED FOODS	Folic Acid ($\mu\text{g}/100\text{g}$)
Breakfast cereals fortified with 100% of the DV, ¾ cup	400
Breakfast cereals, fortified with 25% of the DV, ¾ cup	100
Rice, white, long-grain, parboiled, enriched, cooked, ½ cup	65
Bread, white, 1 slice	25
Bread, whole wheat, 1 slice	25

Recommendations for folate are given in the Dietary Reference Intakes (DRIs) developed by the Institute of Medicine of the National Academy of Sciences at 1998 (99).

The RDAs for folate are expressed in a term called the *Dietary Folate Equivalent*. Dietary folate equivalent (DFE) is a unit of expression for the folate DRIs (except the upper level) (99).

The Dietary Folate Equivalent (DFE) was developed to help account for the differences in absorption of naturally occurring dietary folate and the more bioavailable synthetic folic acid (99,100).

Table 2.2.5.3. lists the RDAs for folate, expressed in micrograms (μg) of DFE, for children and adults (99,100).

The RDA for all adult males and nonpregnant females ≥ 14 years is 400 μg DFE/day, respectively. It is determined that there is an additional requirement of 200 $\mu\text{g}/\text{day}$ during pregnancy and 100 $\mu\text{g}/\text{day}$ during breastfeeding (lactation) (99,100) (TABLE 2.2.5.3.)

There is insufficient information on folate to establish an RDA for infants. An adequate intake (AI) has been established that is based on the amount of folate consumed by healthy infants who are fed breast milk (99).

Table 2.2.5.4 gives the adequate intake for folate, in micrograms (μg) for infants (99).

Table 2.2.5.3. Dietary reference intake values for folic acid by children and adult

Group	RDA ($\mu\text{g DFE/day}$) ^a
■ Children (male & female)	
1-3 years	150
4-8 years	200
■ Adolescent adult males & females	
9-13 years	300
14-18 years	400
19 to \geq 70 years	400
■ Pregnancy	
<18 years	600
19-50 years	600
■ Lactation	
<18 years	500
19-50 years	500

^aAs Dietary Folate Equivalent (DFE)
Sources: Institute of Medicine (1998). National Academy Press. Washington, DC ; Suitor CW & Bailey LB. 2000. *J Am Diet Assoc.* 100, 88-94

Table 2.2.5.4. Dietary Reference Intake Values for Folic acid by Infant

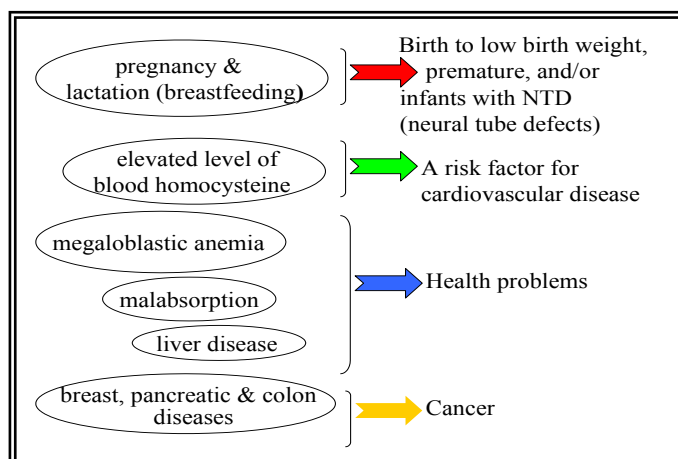
Group	RDA ($\mu\text{g DFE/day}$) ^a
■ Infants (male & female)	
0-6 months	65
7-12 months	80

^aAs Dietary Folate Equivalent (DFE)
Sources: Institute of Medicine (1998). National Academy Press. Washington, DC ; Suitor CW & Bailey LB. 2000. *J Am Diet Assoc.* 100, 88-94

When expressed as DFEs, all forms of dietary folate, including folic acid in fortified products, are converted to an amount that is equivalent to food folate (88). The quantity of synthetic folic acid in the diet is firstly multiplied 1.7 times and this quantity is added to the μg of food folate (88). The conversion factor (1.7) was based on the observation that when folic acid is consumed with a meal, that is the usual case for a fortified product, then the added folic acid is about 85% available and food folate is about 50% available. Therefore the ratio 85:50 yielded the multiplier of 1.7 in the DFE calculation (88).

A recent study provides confirming evidence for the validity of the use of the 1.7 multiplier to correct for the higher bioavailability of folic acid than the naturally occurring food folate (101).

Folate is essentially nontoxic. It is reported that the upper limit of folate is 1000 μg . Deficiency produces megaloblastic anemia indistinguishable from that due to vitamin B₁₂ deficiency. The appearance of this type of anemia is identical to that observed with vitamin B₁₂ deficiency due to the common pathway shared by the folic acid and the active methyl cycles. One major difference between these two deficiencies is the absence of the neurological symptoms from lowered serum folic acid levels (88,94).

**Figure 2.2.5.2.** The major problems in folic acid deficiency

A deficiency of folate can occur when an increased need for folate is not matched by an increased intake, when dietary folate intake does not meet recommended needs, and when folate excretion increases. Medications that interfere with the metabolism of folate may also increase the need for this vitamin and risk of deficiency (102-104).

Folate requirements are increased in pregnant women to meet the demands for DNA synthesis and one carbon transfer reactions in rapidly dividing fetal and maternal cells (88, 105). It is reported that the great risk of low infant birth weight, fetal growth retardation, premature baby, infants with neural tube defects develops if the folic acid intake is restricted or decreased during pregnancy (88, 102-105) (Figure 2.2.5.2.)

The neural tube forms in the developing embryo from the neural plate during the first 28 days postconception and develops into the spinal cord and its protrusion which encases the brain.

2.3. The interactions between most fortified & dietary bioactive vitamins and genomics/vitamin-dependent genes: Nutritional, metabolic and medical aspects

The science of nutrigenomics is the study of how naturally occurring chemicals in foods alter molecular expression of genetic information in each individual. Scientific receptors exist for eicosanoids and vitamins (109-111).

Molecular studies have reported that dietary chemicals or their metabolites bind directly to nuclear receptors (transcription factors) and alter gene expression (TABLE 2.3.1.) (109).

Table 2.3.1. Some nuclear receptors^{a,b}

Steroid	Vitamin	Bile, cholesterol, xenobiotics
Androgen (AR)	Retinoic acid (RAR)	Fransoid X (FXR)
Brassinosteroid (BR)	Retinoid X (RXR)	Liver X (LXR)
Estrogen (ER)	Vitamin D (VDR)	Pregnane X (PXR)
Thyroid	Orphan receptors	Eicosanoid
Thyroid (TXR)	>40 ligands uncharacterized	Peroxisome proliferator activated receptor (PPAR)
^a Some receptors, like PPAR, have several related variants		
^b Source: From Fogg-Johnson & Kaput, 2003 . Nutrigenomics: An Emerging Scientific Discipline. <i>Food Technology</i> , 57 (4), 60-67 ; http://receptors.ucsf.edu/NR/		

Vitamin D, through its daughter metabolite, the steroid hormone $1\alpha,25(\text{OH})_2\text{D}_3$, functions in a manner homologous to that of the classical steroid hormones (112). According to general model, a steroid hormone is produced in an endocrine gland in response to physiological stimulus, then circulates in the blood, generally bound to the carrier DBP (vitamin D-binding protein), to target tissues where the hormone interacts with specific, high affinity intracellular receptors (112). It is known that using the advent of microarray analysis, several hundred genes are regulated by $1\alpha,25(\text{OH})_2\text{D}_3$ (112-114).

By genetic defects in the α -tocopherol transfer protein, vitamin E deficiency is caused. Genetic defects in α -TTP are associated with a characteristic syndrome, ataxia with vitamin E deficiency which characterized neurological abnormalities. It is shown that a dose of 800-1,200 mg/day is usually adequate to prevent further deterioration of neurological functions (8). Vitamin E deficiency is also caused by genetic defects in lipoprotein synthesis. Daily doses of 100-200 mg/kg, or ~5-7 g of RRR- α -tocopherol are recommended regarding the preventing dose for genetic defects in lipoprotein synthesis (8).

Figure 2.3.1. shows that genes associated with folate and clinical conditions (115). It has studied that the administration of 9-cis retinoic acid to such animals brought about no accumulation of the CRBP mRNA (116). So, in spite of vitamin A deficiency, oral administration of corn oil, but not 9-cis retinoic acid, caused an increase in jejunal CRBP mRNA level. It has reported the CRBP gene expression in rat jejunum may be regulated predominantly by dietary Fas, but little by dietary retinoids (117).

It is determined that the physiological action of retinoids is expressed through nuclear receptors which can bind retinoids and regulate the expression of various genes. All *trans*-retinoic acid and 9-cis retinoic acid which are active metabolites of vitamin A are utilized as ligands for nuclear receptors (RAR, RXR), that results in regulation of the expression of various genes at the transcription level (116-117).

The downstream metabolites of retinol, all-*trans* and 9-cis retinoic acids are the bioactive components that bind and activate their cognate nuclear receptors to regulate target genes (118). It has provided detailed information on the specific nuclear receptors, coactivators and chromatin modification events that occur when vitamin A is deficient and, therefore, retinoids are not available to activate the nuclear retinoid-signaling cascade (118).

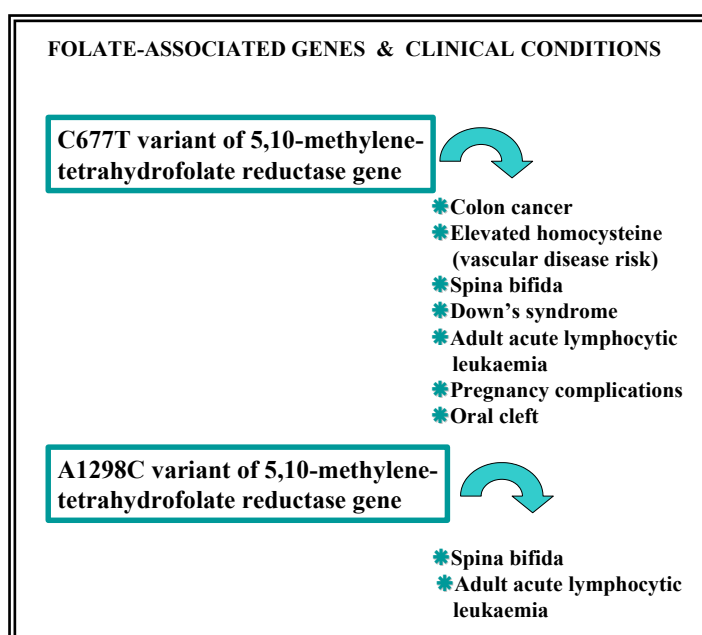


Figure 2.3.1. Genes associated with folate and clinical conditions

Therapeutic effects in hyper proliferative and inflammatory diseases, such as acne, psoriasis, photoaging and neoplasia's are accomplished by the abilities of the biologically active form of vitamin A, retinoic acid and its synthetic analogs to regulate complex programs of gene expression in target cells via binding to nuclear receptors, that are ligand-dependent transcription factors (119).

It is reported that the insulin-like growth factor-I receptor (IGF-IR) has an crucial role in colorectal cancer development and progression (120). Folic acid is a chemopreventive agent whose deficiency has been linked to an enhanced colon cancer risk. IGF-IR displays a potent anti-apoptotic activity and is overexpressed in primary tumors and colon cancer-derived cell lines (120). The regulation of IGF-IR gene expression by folic acid was assessed utilizing RT-PCR, transient transfections and chromatin immunoprecipitation assays (120). It is also determined that folic acid deficiency may lead to increased IGF-IR gene expression, with ensuing pathological activation by endocrine and/or autocrine/paracrine IGF-I (120).

It is reported that the folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring (121).

A. $1\alpha,25$ -dihydroxyvitamin D_3 ($1\alpha,25(OH)_2D_3$) analogs inhibit growth in vitro and in vivo of cells derived from a variety of tumors (122). It has examined that the effects of $1\alpha,25(OH)_2D_3$ and its analog EB1089 on proliferation and target gene regulation of human head and neck squamous cell carcinoma (SCC) lines SCC4, SCC9, SCC15, and SCC25 (1229). The anti proliferative effects of $1\alpha, 25(OH)_2D_3$ and EB1089 in SCC25 cells were analyzed by screening more than 4,500 genes on two cDNA microarrays, yielding 38 up-regulated targets, containing adhesion molecules, growth factors, kinases, and transcription factors (122).

B. Increased NCOR1 mRNA is a novel molecular lesion in breast cancer cells, that acts to suppress responsiveness of VDR target genes, resulting in $1\alpha,25(OH)_2D_3$ resistance and seems to be particularly associated with estrogen receptor negativity (123).The above-mention lesion provides a novel molecular diagnostic and can be targeted via combinations of vitamin D_3 compounds and low doses of trichostatin A (TSA; histone deacetylation inhibitor) (123).

$1\alpha,25$ -Dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] regulates calcium homeostasis and controls cellular differentiation and proliferation (124). The vitamin D receptor (VDR) is a ligand-regulated transcription factor that recognizes cognate vitamin D response elements (VDREs) formed by direct or everted repeats of PuG(G/T)TCA motifs separated by 3 or 6 bp (DR3 or ER6) (124). It has identified that direct $1,25(OH)_2D_3$ target genes by combining 35,000+ gene microarrays and genome-wide screens for consensus DR3 and ER6 elements, and DR3 elements containing single nucleotide substitutions (124).

It has reported the interaction of vitamin D and retinoid receptors on regulation of gene expression (125). Vitamin D and retinoic acid (RA) receptors (VDRs and RARs, respectively), bind as heterodimers with the retinoid X receptor (RXR) to hormone response elements (HREs) in target genes (125).

Vitamin D-influenced gene expression by a ligand-independent, receptor-DNA complex intermediate has reported (126). It has shown that vitamin D receptor (VDR), derived from extracts of the small intestines of

vitamin D-deficient rats, is capable of binding a vitamin D response element (DRE) by an electrophoretic mobility-shift analysis (126).

It has found that $1,25(\text{OH})_2\text{D}_3$ most substantially increased the expression of the insulin-like growth factor binding protein-3 (*IGFBP-3*) gene (127). Additionally, was found that, some of the key genes regulated via $1,25(\text{OH})_2\text{D}_3$ are also androgen-responsive genes (127). The up-regulation of *IGFBP-3* gene has been shown to be important in $1,25(\text{OH})_2\text{D}_3$ -mediated inhibition of LNCaP cell growth. The putative $1,25(\text{OH})_2\text{D}_3$ target genes appear to be involved in various of cellular functions containing growth regulation, differentiation, membrane transport, cell-cell and cell-matrix interactions, DNA repair, and inhibition of metastasis (127).

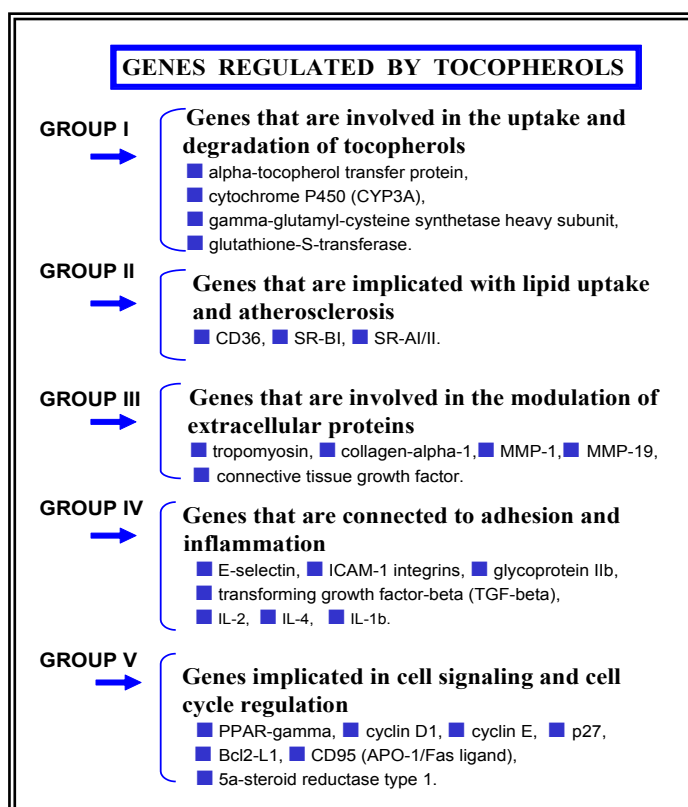


Figure 2.3.2. Genes regulated by tocopherols.

Several genes are regulated by tocopherols partly due to the effects of tocopherol on these two kinases (protein kinase C and phosphatidylinositol 3-kinase), but also independently of them (128). Genes regulated by tocopherols can be divided in five groups (128). Figure 2.3.2. shows the several genes regulated by tocopherols. Group I, group II, group III, group IV and group V of genes contains genes that are involved in the uptake and degradation of tocopherols, genes that are implicated with lipid uptake and atherosclerosis, genes that are involved in the modulation of extracellular proteins, genes that are connected to adhesion and inflammation, genes implicated in cell signaling and cell regulation, respectively (Figure 2.3.2.).

The regulation of genes via tocopherols has been associated with protein kinase C owing to its deactivation by α -tocopherol and its contribution in the regulation of a number of transcription factors (NF-kappaB, AP1) (128).

It is known that T cells are vulnerable to age-associated changes. Vitamin E has been shown to improve T cell functions in the old. It is reported that gene expression profiles of T cells to better understand the underlying mechanisms of age and vitamin E-induced changes in T cell function (129). According to performed experiments with young and old C57BL mice, 500 ppm of vitamin E supplementation for 4 wks resulted in higher expression of genes involved in cell cycle regulation (*Ccnb2*, *Cdc2*, *Cdc6*) in old T cells. Gene expression profiles of T cells were assessed utilizing microarray analysis with/without anti-CD3/anti-CD28 stimulation (129). It has found that vitamin E supplementation resulted in higher up-regulation of IL-2 expression in young and old T cells whereas lower up-regulation of IL-4 expression in old T cells following stimulation and also resulted in higher up-regulation of IL-2 expression in young and old T cells whereas lower up-regulation of IL-4 expression in old T cells following stimulation (129). It has suggested that aging has significant effects regarding the gene expression associated with signal transduction, transcriptional regulation and apoptosis pathways in T cells and vitamin E has a significant impact concerning the gene expression associated with cell cycle and Th1/Th2 balance in old T cells (129).

References

1. Gregory III JF. 1996. Vitamins. In Food Chemistry. Fennema O.R. (eds). Marcel Dekker, Inc. New York. p.531-616. ISBN: 0-8247-9346-3.
2. de Man JM. 1999. Principles of Food Chemistry. Aspen Publishers, Inc. Gaithersburg, Maryland. p. 362-365; 355-388. ISBN: 0-8342-1234-X
3. Combs GF. 1996. Should intakes with beneficial actions, often requiring supplementation, be considered for RDAs? *J Nutr* 126: 2373S-2376S.
4. Fenech M. 2007. Nutrition and Genome Health. In *Nutrigenomics-Opportunities in Asia*. Tai ES, Gillies PJ (eds). Forum Nutr. Basel, Karger, 2007, vol 60, pp 49-65.
5. Gerster H. 1991. Potential role of α -carotene in the prevention of cardiovascular disease. *Int J Vitam Nutr Res*, 61, 277-291.
6. Germann I. 1990. Antioxidant Vitamins and Cardiovascular Diseases. Hoffmann-La Roche, Basel, Switzerland.
7. Simon JA. 1992. Vitamin C and cardiovascular disease: a review. *J. Am. Coll. Nutr.*, 11, 107-125.
8. Traber MG. 2007. Vitamin E. In *Handbook of Vitamins*. Zempleni J, Rucker RB, Mc Cormick DB, Suttie JW. 4th edition. p:153-174. CRC Press, Taylor & Francis Group, Boca Raton, FL. ISBN-13: 978-0-8493-4022-2.
9. Kamal-Eldin A, Appelqvist LA. 1996. The chemistry and antioxidant properties of tocopherols and tocotrienols. *Lipids*, 31, 671.
10. Tokuşođlu Ö, Özcan C, Akşit S, Tansuđ N, Dinç G, Kasırđa E. 2006. Fatty acid contents, vitamin distribution and occurrence of mycotoxins in breast milk: Studies on the determination of interactions between mothers' maternal diet and plasma levels. Research fund project report. Project No: 2004/025. Celal Bayar University Scientific Research Projects Commission, Manisa, Turkey.
11. Alkhenizan A, Hafez K. 2007. The role of vitamin E in the prevention of cancer: a meta-analysis of randomized controlled trials. *Ann Saudi Med*. 27(6): 409-414.
12. Valastyan S, Thakur V, Johnson A, Kumar K, Manor D. 2008. Novel transcriptional activities of vitamin E: inhibition of cholesterol biosynthesis. *Biochemistry*. 47(2): 744-752.
13. <http://www.nap.edu/catalog.php>. 2008. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids.
14. National Research Council. 1989. Fat soluble vitamins. In: *Recommended Dietary Allowances*. 10th ed. Washington, DC: National Academy of Sciences, p.78-114.
15. Akalın S., Tokuşođlu Ö. 2004. "Liquid Chromatographic Detection of α -, β -, γ -Tocopherols in Infant Formulas". *Milchwissenschaft*, 59(5/6) 244-246.
16. Machlin LJ. 1995. Critical assessment of the epidemiological data concerning the impact of antioxidant nutrients on cancer and cardiovascular disease. *Crit. Rev. Food Sci. Nutr.* 35(1-2) 41-50
17. Virtamo J. 1999. Vitamins and lung cancer. *Proc. Nutr. Soc.* 58(2), 329-333.
18. Caragay AB. 1992. Cancer-preventive foods and ingredients. *Food Technol.* 46(4): 65-68.
19. Duell PB. 1996. Prevention of Atherosclerosis with Dietary Antioxidants: Fact or Fiction? *J. Nutr.* 126, 1067S-1071S.
20. Janero DR. 1995. Ischemic heart disease and antioxidants: mechanistic aspects of oxidative injury and its prevention. *Crit. Rev. Food Sci. Nutr.* 35(1-2):65-81.
21. van Poppel G., van den Berg H. 1997. Vitamins and cancer. *Cancer Lett.* 114(1-2):195-202.
22. Sies H, Stahl W. 1995. Vitamins E and C, beta-carotene, and other carotenoids as antioxidants. *Am. J. Clin. Nutr.* 62: 1315S-1321S
23. EC.: Commission Directive 91/321/EC/ of 14 May 1991 on infant formulae and follow-on formulae No. L175, European Commission, Brussels, 4 July, 1991, p.35 (1991).
24. EC. 1996. Directiva relativa a los preparados para lactantes y preparados de continuacion. 96/4/CE. Diario Oficial de las Comunidades Europeas. L49: 12-16.
25. USDA. 2006. U.S. Department of Agriculture, Agricultural Research Service, Nutrient Data Laboratory. <http://www.nal.usda.gov/fnic/foodcomp>
26. Tokusoglu Ö. 2007. "Green Gold: Pistachionut. Technology, Chemistry and Quality Control" Sonmez Publisher. 86 page. ISBN: 978-9944-60-161-0.
27. Tokuşođlu Ö, Durucasu İ, Yemiş F, Yıldırım Z. 2003. "High Performance Liquid Chromatographic Determination of Seed D-form (RRR-) Tocopherol Homologues of Sesame (Sesamum Indicum L.) Spreads: Process Effects on their Quantities". *J. Food Technol.*, 1 (3): 97-101.
28. Thaler H. 1967. Concentration and stability of tocopherols in foods. In *Tocopherol*, ed. K. Lang. Darmstadt, Germany: Steinkopff Verlag.
29. Eitenmiller RR. 1997. Vitamin E content of fats and oils: Nutritional implications. *Food Technol.* 51(5): 78-81.
30. Konings EJM, Roomans HHS, Beljaars PR. 1996. *J AOAC Int.* 79, 902.
31. Tokuşođlu Ö, Tansuđ N, Akşit S, Dinç G, Kasırđa E, Özcan C. 2008. Retinol and alpha-tocopherol concentrations in breast milk of Turkish lactating mothers under various socio-economic status. *Int. J. Food Sci. Nutr.* 59(2), 166-174.
32. Hashim SA, Asfour RH. 1968. Tocopherol in infant fed diets rich in polyunsaturated fatty acids. *Am J Clin Nutr.* 21(1): 7-14
33. Lammi-Keefe C.J. & Jensen R.G. 1984. Fat-soluble vitamins in human milk. *Nutr. Rev.* 42, 365-369.
34. Gross R, Hansel H, Schultink W, Shrimpton R. 1998. Moderate zinc and vitamin A deficiency in breast milk of mothers from East-Jakarta. *Eur J Clin Nutr* 52(12): 884-890.
35. Bohm V, Peiker G, Starker A, Weske F. 1997. Vitamin B1, B2, A and E and beta-carotene content in transitional breast milk and comparative studies in maternal and umbilical cord blood. *Z. Ernährungswiss.* 36(3): 214-219.
36. Zheng MC, Zang Gf, Zhou LS, Guo XG, Quan YF. (1993). Alpha-tocopherol concentrations in human milk from mothers of preterm and full-term infants in China. *Biomed Environ Sci* 6(3): 259-264.
37. Food and Nutrition Board. 2000. Institute of Medicine in *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, Carotenoids*, National Academy Press, Washington, p.186-283.
38. Landrum JT, Bone RA, Joa H, Kilburn MD, Moore LL, Sprague KE. 1997. A one year study of the macular pigment: the effect of 140 days of a lutein supplement. *Exp Eye Res* 65(1):57-62.

39. Mares-Perlman JA, Millen AE, Ficek TL, Hankinson SE. 2002. The body of evidence to support a protective role for lutein and zeaxanthin in delaying chronic disease. Overview. *J.Nutr.* 132, 518S-524S.
40. Alves-Rodrigues A, Thomas B. 2002. The role of lutein in the prevention of atherosclerosis. *J. Am. Coll. Cardiol.*, 40, 835-836.
41. Alves-Rodrigues A, Shao Andrew. 2004. The Science Behind Lutein. *Toxicology Letters.* 150, 57-83.
42. Mayne ST. 1996. Beta-carotene, carotenoids, and disease prevention in humans. *FASEB J.*; 10:690-701.
43. Mortensen A, Skibsted LH, Sampson J, Rice-Evans C, Everett SA. 1997. Comparative mechanisms and rates of free radical scavenging by carotenoid antioxidants. *FEBS Letters* 418: 91-97.
44. U.S. Department of Agriculture, Agricultural Research Service. 1998. USDA-NCC Carotenoid Database for U.S. Foods. Nutrient Data Laboratory Homepage. <http://www.nal.usda.gov/fnic/foodcomp>
45. Hart DJ, and Scott KJ. 1995. Development and evaluation of an HPLC method for the analysis of carotenoids in foods, and the measurement of the carotenoid content of vegetables and fruits commonly consumed in the UK. *Food Chem*, 54:101-11.
46. Handelman Garry J, Zachary D, Nightingale, Alice H, Lichtenstein, Ernst J, Schaefer and Jeffrey B, Blumberg. 1999. Lutein and zeaxanthin concentrations in plasma after dietary supplementation with egg yolk. *Am J Clin Nutr*, 70 (2), 247-251
47. Schlatterer Jörg, Breithaupt Dietmar E. 2006. Xanthophylls in Commercial Egg Yolks: Quantification and Identification by HPLC and LC-(APCI)MS Using a C30 Phase. *J.Agric.Food Chem.*, 54, 2267-2273.
48. Packer L. 1993. Antioxidant action of carotenoids in vitro and in vivo and protection against oxidation of human low-density proteins. In L.M. Canfield, N.L. Crinsky, J.A. Olson. *Carotenoids in human health. Annals of the New York Academy of Sciences (Vol.691).*
49. Rybski J.A., Grogan T.M., Aickin M. & Gensler H. 1991. Reduction of murine cutaneous UVB-induced tumour-infiltrating T lymphocytes by dietary canthaxanthin. *Journal of Investigational Dermatology.* 97, 892-897.
50. Tokusoglu Ö, Alakir İ. (2006). Lutein/Zeaxanthine Ratio In Industrial Egg Yolks By Heat Process Effects and The Evaluations From The Public Health of View. 4th Euro Fed Lipid Congress - Fats, Oils and Lipids for a Healthier Future, 01-04 October 2006, Madrid, SPAIN, 2006. Poster Presentation.
51. Ross CA, Harrison EH. 2007. Vitamin A: Nutritional Aspects of Retinoids and Carotenoids. In *Handbook of Vitamins.* Zemleni J, Rucker RB, McCormick DB, Suttie JW. 4th edition. p:1-39. CRC Press, Taylor & Francis Group, Boca Raton, FL. ISBN-13: 978-0-8493-4022-2.
52. Ball GFM. 2000. The Fat-Soluble Vitamins. In *Food Analysis by HPLC.* 2nd edition. Ed. Leo ML Nollet, Marcel Dekker Inc., New York. ISBN.0-8247-8460-X
53. Institute of Medicine. 2002. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. National Academy Press: Washington, 2002, p.8-9.
54. Greer FR. 2001. Do breastfed infants need supplemental vitamins? *Pediatr Clin North Am* 48: 415-425.
55. Picciano MF. 2001. Nutrient composition of human milk. *Pediatr Clin North Am* 48:53-58.
56. Astorg P. 1997. Food carotenoids and cancer prevention: An overview of current research. *Trends Food Sci Tech*, 8, 406-413.
57. Tokusoglu Ö., Alakir I. 2007. The determination of lutein, zeaxanthin, canthaxanthin xanthophylls in egg yolk and interactions between Hunter L*a*b* color parameters: The researches on the determination of heat process effects. Research Fund Project, No: 2005/011, Celal Bayar University, Manisa, Turkey. 163 p.
58. Holden JM, Eldridge AL, Beecher GR. 1999. Carotenoid content of U.S. foods: an update of the database. *J Food Comp Anal* 12, 169-196.
59. Rouseff RL, Nagy S. 1994. Health and nutritional benefits of citrus fruit components. *Food Technol* 48(11), 126-132.
60. Abushita AA., Emhemed AH, Hussein GD, Péter AB. 1997. Determination of antioxidant vitamins in tomatoes. *Food Chem*, 60 (2): 207-212.
61. Böhm V, Fröhlich K, Roland B. 2003. Rosehip-a new source of lycopene. *Molecular Aspects of Medicine*, 24, 385-389.
62. USDA. 1998. (U.S. Department of Agriculture), Agricultural Research Service, 1998. USDA-NCC Carotenoid Database for U.S. Foods 1998. Nutrient Data Laboratory Homepage <http://www.nal.usda.gov/fnic/foodcomp>.
63. Chow CK. 2000. Vitamin E. In: Stipanuk MH (Ed.), *Biochemical and Physiological Aspects of Human Nutrition.* WB.Saunders Company, Philadelphia PA, pp.584-596.
64. Noy N. 2000. Vitamin A. In: Stipanuk MH (Ed.), *Biochemical and Physiological Aspects of Human Nutrition.* WB.Saunders Company, Philadelphia PA, pp.599-618.
65. Yeum KJ, Russell RM. 2002. Carotenoid bioavailability and bioconversion. *Annu Rev Nutr* 22, 483-504.
66. USDA. 2004. USDA Nutrient Database for Standard Reference, Laboratory, Agricultural Research Service, 2004, <http://www.nal.usda.gov/fnic/foodcomp/search/>.
67. Demirci M. 2004. Vitamins. In *Food Chemistry.* Tekirdağ University Publishment. 2nd edition. p.99-112. ISBN: 975-97146-2-0.
68. West CE. 2000. Meeting requirements for vitamin A. *Nutr Rev* 58(11):341-5. PMID:16120.
69. USDA. 2004. What we eat in America. Citation: U.S. Department of Agriculture, Agriculture Research Service. 2004. NHANES 2001-2002: Documentation and Data Files. <http://www.ars.usda.gov/bahnr/fsrg>.
70. World Health Organization. 1996. Indicators for assessing vitamin A deficiency and their application in monitoring and evaluating intervention programmes. Document WHO/NUT/96.10. Geneva: WHO
71. WHO, Prevention and control of vitamin A deficiency, xerophthalmia and nutritional blindness. In: Proposal for a Ten-Year Programme of Support to Countries, ed. Organization, Geneva: WHO, Doc. NUT / 84.5 Rev 1, 1985, As cited at: <http://www.unsystem.org/scn/archives/rwns01/ch10.htm>.
72. Sommer A. 1993. Vitamin A, infectious disease, and childhood mortality. *J. Infect. Dis.* 167, 1003.
73. D'Souza RM, D'Souza R. 2002. Vitamin A for the treatment of children with measles-a systematic review. *J. Trop. Pediatr.* 48, 323.

74. WHO/UNICEF. 1987. Vitamin A for measles. *Lancet*, 2, 1067.
75. Committee on Infectious Diseases. 1993. Vitamin A treatment of measles. *Pediatrics*.91(5), 1014-1015.
76. Grant WB, Garland CF. 2004. *Nutr Cancer*. A critical review of studies on vitamin D in relation to colorectal cancer. *Nutr Cancer*. 48(2):115-23.
77. Giovannucci E. 2005. *Cancer Causes Control*. 16(2):83-95. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States).
78. Cranney A, Horsley T, O'Donnell S, Weiler H, Puil L, Ooi D, Atkinson S, Ward L, Moher D, Hanley D, Fang M, Yazdi F, Garrity C, Sampson M, Barrowman N, Tsertsvadze A, Mamaladze V. 2007. Effectiveness and safety of vitamin D in relation to bone health. *Evid Rep Technol Assess.* (158):1-235.
79. Rene FC , Hong C , Lorrie B , Connie S , John SA. 2007. Cloning, sequencing, and functional characterization of the vitamin D receptor in vitamin D-resistant New World primates. *The Prostate*, 67 (9) , 911 – 923.
80. Antonio Z. 2006. a <http://www.nap.edu.catatlog>. Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.
81. USDA. 2003. United States Department of Agriculture, Agricultural Research Service, National Nutrient Database for Standard Reference, Release 16. http://www.nal.usda.gov/fnic/cgi-bin/nut_search.pl., Bethesda, MD, US Department of Agriculture.
82. Food and Nutrition Board (FNB). 1997. Dietary reference intakes for calcium, magnesium, phosphorus, vitamin D, and fluoride. Ed. Institute of Medicine. National Academy of Sciences.
83. Webb AR, Holick MF. 1988. The role of sunlight in the cutaneous production of vitamin D3. *Ann.Rev.Nutr.*,8, 375.
84. Oliveri MB, Mautalen C, Bustamante L, Gomez GV. 1994. Serum levels of 25-hydroxyvitamin D in a year of residence on the Antarctic continent. *Eur.J.Clin.Nutr.*, 48, 397.
85. Engelsen O., Brustad M., Aksnes L., and Lund E. 2005. Daily duration of vitamin D synthesis in human skin with relation to latitude, total ozone, altitude, ground cover, aerosols and cloud thickness. *Photochem. Photobiol.*, 81, 1287.
86. Lips P. 2004. Which circulating level of 25-hydroxyvitamin D is appropriate □ *J.Steroid Biochem.Mol.Biol.*, 89-90, 611.
87. Russell LF. 2000. Quantitative Determination of Water Soluble Vitamins. VII.Folacin. In *Food Analysis by HPLC*. 2nd edition. Ed.Leo ML Nollet, Marcel Dekker Inc.,NewYork. ISBN.0-8247-8460-X
88. Bailey LB. 2007. Folic Acid. In *Handbook of Vitamins*. Zempleni J, Rucker RB, Mc Cormick DB, Suttie JW.4th edition. p:153-174.CRC Press , Taylor & Francis Group, Boca Raton, FL. ISBN-13: 978-0-8493-4022-2.
89. Brody T. 1991. Folic Acid. In: *Handbook of Vitamins*. LJ Machlin (ed.) 2nd ed. New York: Marcel Dekker, pp.453-489.
90. Mulinare J.1995.Public health perspectives on folic acid and neural tube defects. *Cereal Foods World*, 40:58-61.
91. Bower C. 1995. Folate and neural tube effects. *Nutr.Rev.*, 53, S33-S38.
92. Ubbinck JB, Becker PJ, Vermaak WJH. 1996. Will an increased dietary folate intake reduce the incidence of cardiovascular disease □ *Nutr.Rev.* 54, 213-216.
93. Butterworth CE. 1992. Effect on folate on cervical cancer: synergism among risk factors. *Ann.NY.Acad.Sci.* 669, 293-299.
94. Antonio Z. 2006. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. <http://www.nap.edu.catatlog>.
95. Rose RC. 1996. Intestinal absorption of water-soluble vitamins. *Proc.Soc.Exp.Biol.Med.USA*, 212, 191-198.
96. Gregory JF.1995. The bioavailability of folate. In *Folate in Health and Disease.*, Bailey, L., ed.,Marcel Dekker, New York. pp.195-235.
97. Bailey LB.1995. Folate requirements and dietary recommendations. In *Folate in Health and Disease*, Bailey LB (ed.), Marcel Dekker, New York, pp.123-151.
98. FS. 1996. Food Standards: amendment of standards of identity for enriched grain products to require addition of folic acid, Final rule. 21 CFR Parts 136,137, and 139, in *Fed. Regist.*, pp.8781-8789.
99. Institute of Medicine. 1998. Food and Nutrition Board. Dietary Reference Intakes: Thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. National Academy Press. Washington, DC.
100. Suitor CW, Bailey LB. 2000. Dietary folate equivalents: Interpretation and application. *J Am Diet Assoc.* 100, 88-94.
101. Yang TL, Hung J, Caudill MA, Urrutia TF, Alamila A, Perry CA, Li R, Hata H, Cogger EA. 2005. A long-term controlled folate feeding study in young women supports the validity of the 1.7 multiplier in the dietary folate equivalency equation. *J.Nutr.*, 135(5), 1139-1145.
102. NIH. 2008. Dietary Supplement Fact Sheet: Folate. In *Office of Dietary Supplements of National Institute of Health.*, Bethesda, Maryland 20892, USA.
103. McNulty H. 1995. Folate requirements for health in different population groups. *Br J Biomed Sci*, 52, 110-119.
104. Kelly GS. 1998. Foliates: Supplemental forms and therapeutic applications. *Altern Med Rev*, 3, 208-220.
105. Scholl TO, Johnson WG. 2000. Folic acid: influence on the outcome of pregnancy. *Am J.Clin.Nutr.*, 71 (5 Suppl), 1295S-1303S.
106. Kloosterman J, Franssen Heidi P, de Stoppelaar J, Verhagen H, Rempelberg C. 2007. Safe addition of vitamins and minerals to foods: setting maximum levels for fortification in the Netherlands. *Eur J Nutr*, 46, 220-229.
107. Tokuşoğlu Ö. 2006. Fortification Criteria of Vegetable Oils and Margarines with Alpha-Tocopherol and Tocopheryl Acetate: The Regulations on Vitamin E Labeling. Lecture. In *World Conference and Exhibition on Oilseed and Vegetable Oil Utilization, Processing, By-Products, Biodiesel, Specialty and Functional Oils, and New Applications & Technologies* 14-16 August 2006, Istanbul.
108. Scientific Committee on Food and Scientific Panel on Dietetic Products, Nutrition and Allergies. 2006. Tolerable upper intake levels for vitamins and minerals. European Food Safety Authority.
109. Fogg-Johnson N, Kaput J. 2003. Nutrigenomics: An Emerging Scientific Discipline. *Food Technology*, 57 (4), 60-67.
110. Aranda A, Pascual A. 2001. Nuclear hormone receptors and gene expression. *Physiol.Rev.*, 81, 1269-1304.
111. <http://receptors.ucsf.edu/NR>

112. Norman AW, Henry HL. 2007. Vitamin D. In Handbook of Vitamins. Zemleni J, Rucker RB, Mc Cormick DB, Suttie JW. 4th edition. p:41-109. CRC Press, Taylor & Francis Group, Boca Raton, FL. ISBN-13: 978-0-8493-4022-2.
113. Norman AW, Xu J, Collins ED. 2002. The vitamin D endocrine system: Metabolism, mode of action, and genetic evaluation. In: Genetics in Endocrinology, Ed. Baxter J.D., p.445. Lippincott-Raven, Philadelphia, PA.
114. White JH. 2004. Profiling 1,25-dihydroxyvitamin D₃-regulated gene expression by microarray analysis. *J. Steroid Biochem. Mol. Biol.* 89-90, 239.
115. Lucock M. 2004. Is folic acid the ultimate functional food component for disease prevention? *Clinical Review. BMJ*, 328, 211-214.
116. Takase S, Tanaka K, Suruga K, Kitagawa M, Igarashi M, Goda T. 1998. Dietary fatty acids (Fas) are possible key determinants of cellular retinol-binding protein II gene expression. *American Journal of Physiology*, 274, G626-G632.
117. Takase S, Suruga K, Goda T. 2000. Regulation of vitamin A metabolism-related gene expression. *British Journal of Nutrition*, 84(2), S217-S221.
118. McGrane M. 2003. Vitamin A regulation of gene expression: molecular mechanism of a prototype gene. *The Journal of Nutritional Biochemistry* 18 (8), 497 - 508.
119. Nagpal S, Chandraratna RA. 1998. Vitamin A and regulation of gene expression. *Curr Opin Clin Nutr Metab Care.* 1(4), 341-346.
120. Attias Z, Werner H, Vaisman N. 2006. Folic acid and its metabolites modulate IGF-I receptor gene expression in colon cancer cells in a p53-dependent manner. *Endocrine-Related Cancer* 13 (2), 571-581.
121. Lillycrop KA, Phillips ES, Jackson AA, Hanson MA, Burdge GC. 2005. Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring. *J Nutr.* 135(6), 1382-1386.
122. Akutsu N, Lin R, Bastien Y, Bestawros A, Enepekides DJ, Black MJ, White JH. 2001. Regulation of Gene Expression by 1,25-Dihydroxyvitamin D₃ and Its Analog EB1089 under Growth-Inhibitory Conditions in Squamous Carcinoma Cells *Molecular Endocrinology* 15 (7), 1127-1139.
123. Banwell CM, MacCartney DP, Guy M, Miles AE, Uskokovic MR, Mansi J, Stewart PM, O'Neill LP, Turner BM, Kay W, Colston KW, Campbell MJ. 2006. Altered Nuclear Receptor Corepressor Expression Attenuates Vitamin D Receptor Signaling in Breast Cancer Cells. *Clinical Cancer Research*, 12, 2004-2013.
124. Tian-Tian Wang TT, Tavera-Mendoza LE, Laperriere D, Libby E, MacLeod NB, Nagai Y, Bourdeau V, Konstorum A, Lallemand B, Zhang R, Mader S, White JH. 2005. Large-Scale in Silico and Microarray-Based Identification of Direct 1,25-Dihydroxyvitamin D₃ Target Genes *Molecular Endocrinology* 19 (11), 2685-2695.
125. Jimenez-Lara AM, Aranda A. 2000. Interaction of Vitamin D and Retinoid Receptors on Regulation of Gene Expression *Hormone Research*, 54 (5-6), 301-305.
126. Ross TK, Darwish HM, Moss VE, DeLuca HF. 1993. Vitamin D-Influenced Gene Expression via a Ligand-Independent, Receptor-DNA Complex Intermediate. *Proceedings of the National Academy of Sciences*, 90, 9257-9260.
127. Krishnan AV, Shinghal R, Raghavachari N, Brooks JD, Peehl DM, Feldman D. 2004. Analysis of vitamin D-regulated gene expression in LNCaP human prostate cancer cells using cDNA microarrays. *The Prostate*, 59(3), 243-251.
128. Azzi A, Gysin R, Kempná P, Munteanu A, Negis Y, Villacorta L, Visarius T, Zingg JM. 2004. Vitamin E mediates cell signaling and regulation of gene expression. *Ann N Y Acad Sci.* 1031, 86-95.
129. Han SN, Adolfsson O, Lee CK, Prolla TA, Ordovas J, Meydani SN. 2006. Age and Vitamin E-Induced Changes in Gene Expression Profiles of T Cells. *The Journal of Immunology*, 177, 6052-6061.

Dual Darboux Frame of a Spacelike Ruled Surface and Darboux Approach to Mannheim Offsets of Spacelike Ruled Surfaces

Mehmet Önder^{1*}, H. Hüseyin Uğurlu²

Abstract

In this paper, we define dual Darboux frame of a spacelike ruled surface. Then, we study Mannheim offsets of spacelike ruled surfaces in dual Lorentzian space by considering the E. Study Mapping. We represent spacelike ruled surfaces by dual Lorentzian unit spherical curves and define Mannheim offsets of the spacelike ruled surfaces by means of dual Darboux frame. We obtain relationships between the invariants of Mannheim spacelike offset surfaces and offset angle, offset distance. Moreover, we obtain some conditions for Mannheim offsets of spacelike ruled surfaces to be developable.

AMS: 53A25, 53C40, 53C50.

Keywords: Spacelike ruled surface; Mannheim offset; dual Darboux frame.

1. Introduction

In differential geometry, a surface is said to be “ruled” if through every point of the surface there is a straight line that lies on the surface. Then, a ruled surface can locally be described as the set of points swept by a moving straight line. For example, a cone is formed by keeping one point of a line fixed whilst moving another point along a circle. Because of they are one of the simplest objects in geometric modeling, these surfaces are largely used in surface theory and also used in many areas of science such as Computer Aided Geometric Design (CAGD), mathematical physics, moving geometry, kinematics for modeling the problems and model-based manufacturing of mechanical products. For example, a wood used as a building material is straight and can be considered as a straight line. So, the engineers can use ruled surfaces if they plan to construct a material with curvature [9].

An offset surface is a surface obtained by using a reference surface’s normal. Offsetting of curves and surfaces is one of the most important geometric operations in CAD/CAM due to its immediate applications in geometric modeling, NC machining, and robot navigation [5]. Especially, the offsets of the ruled surfaces have an important role in (CAGD) [15,16]. The well-known offset of the ruled surfaces is Bertrand offsets which were defined by Ravani and Ku by considering a generalization of the theory of Bertrand curve for trajectory ruled surfaces in line geometry [17]. Moreover, there exists a one-to-one correspondence between the lines of line space and the points of dual unit sphere. This famous correspondence is known as E. Study Mapping [2]. Hence, the geometry of ruled surfaces can be studied by considering dual curves lying on dual unit sphere. An example of this

notion was given by Küçük and Gürsoy for the integral invariants of closed Bertrand trajectory ruled surfaces [7]. They have studied Bertrand offsets of closed ruled surfaces in dual space and introduced some relationships for these surface offsets.

Recently, a new definition of special curve couple was given by Wang and Liu [22]. They have called these curves as Mannheim partner curves. Then, Orbay and et al have given a generalization of the theory of Mannheim partner curves to the ruled surface and called Mannheim offset [9]. They have obtained the conditions for Mannheim offset surfaces to be developable. The corresponding characterizations of Mannheim offsets of ruled surfaces in Minkowski 3-space have been given in ref. [10,14]. Furthermore, in [11] Önder and Uğurlu have studied Mannheim offsets of ruled surfaces in dual space with Blaschke approach and obtained the relations between the integral invariants of closed ruled surfaces. Moreover, they have shown that the striction lines of developable Mannheim offset surfaces are Mannheim partner curves. They have also studied the Mannheim offsets of ruled surfaces in dual Lorentzian space by considering the Blaschke frame [12]. Also, they have given the dual Darboux frame of the timelike ruled surfaces with timelike rulings and studied the Mannheim offsets of these surfaces [13].

In this paper, we define the dual Darboux frame of a spacelike ruled surface and give the real and dual curvatures of this surface. Then, we introduce the Mannheim offsets of the spacelike ruled surfaces in view of dual Darboux frame. Using the dual representations of spacelike ruled surfaces, we give

some theorems and new results which characterize the developable Mannheim spacelike surface offsets and

we give a new relationship between the developable Mannheim offsets and their striction lines

2. Preliminaries

3-dimensional Minkowski space IR_1^3 is the real vector space IR^3 provided with the standard flat metric given by

$$\langle \vec{a}, \vec{a} \rangle = -a_1 b_1 + a_2 b_2 + a_3 b_3,$$

where $\vec{a} = (a_1, a_2, a_3)$ and $\vec{b} = (b_1, b_2, b_3) \in IR^3$. The Lorentzian character of a vector $\vec{a} = (a_1, a_2, a_3)$ is defined as follows:

- i) \vec{a} is called timelike if $\langle \vec{a}, \vec{a} \rangle < 0$,
- ii) \vec{a} is called spacelike if $\langle \vec{a}, \vec{a} \rangle > 0$ or $\vec{a} = 0$,
- iii) \vec{a} is called lightlike (null) if $\langle \vec{a}, \vec{a} \rangle = 0$ and $\vec{a} \neq 0$.

Similarly, the Lorentzian character of a curve $\alpha(s)$ in IR_1^3 is given by considering its velocity vectors $\alpha'(s)$. Then a curve $\alpha(s)$ has the same character with its velocity vector $\alpha'(s)$ [8]. The norm of a vector \vec{a} is defined by $\|\vec{a}\| = \sqrt{|\langle \vec{a}, \vec{a} \rangle|}$. The Lorentzian cross product of two vectors $\vec{a} = (a_1, a_2, a_3)$ and $\vec{b} = (b_1, b_2, b_3)$ is defined by

$$\vec{a} \times \vec{b} = \begin{vmatrix} \vec{e}_1 & -\vec{e}_2 & -\vec{e}_3 \\ a_1 & a_2 & a_3 \\ b_1 & b_2 & b_3 \end{vmatrix} = (a_2 b_3 - a_3 b_2, a_1 b_3 - a_3 b_1, a_2 b_1 - a_1 b_2)$$

where

$$\delta_{ij} = \begin{cases} 1 & i = j, \\ 0 & i \neq j, \end{cases} \quad \vec{e}_i = (\delta_{i1}, \delta_{i2}, \delta_{i3}) \quad \text{and} \quad \vec{e}_1 \times \vec{e}_2 = -\vec{e}_3, \quad \vec{e}_2 \times \vec{e}_3 = \vec{e}_1, \quad \vec{e}_3 \times \vec{e}_1 = -\vec{e}_2.$$

By using this definition it can be easily shown that $\langle \vec{a} \times \vec{b}, \vec{c} \rangle = -\det(\vec{a}, \vec{b}, \vec{c})$ [20].

The sets of the unit timelike and spacelike vectors are called hyperbolic unit sphere and Lorentzian unit sphere, respectively, and denoted by

$$H_0^2 = \{ \vec{a} = (a_1, a_2, a_3) \in IR_1^3 : \langle \vec{a}, \vec{a} \rangle = -1 \}$$

and

$$S_1^2 = \{ \vec{a} = (a_1, a_2, a_3) \in IR_1^3 : \langle \vec{a}, \vec{a} \rangle = 1 \}$$

respectively (See [18]).

Lorentzian character of a surface is defined using its normal vector. Then a surface in IR_1^3 is called a timelike (spacelike) surface if the normal vector of the surface is a spacelike (timelike) vector [1].

3. Dual Numbers and Dual Lorentzian Vectors

Let the set of the pairs (a, a^*) be $D = \mathbb{R} \times \mathbb{R} = \{\bar{a} = (a, a^*) : a, a^* \in \mathbb{R}\}$. For $\bar{a} = (a, a^*)$, $\bar{b} = (b, b^*) \in D$ the following operations are defined on D :

$$\text{Equality} \quad : \quad \bar{a} = \bar{b} \Leftrightarrow a = b, \quad a^* = b^*$$

$$\text{Addition} \quad : \quad \bar{a} + \bar{b} = (a + b, \quad a^* + b^*)$$

$$\text{Multiplication} \quad : \quad \bar{a}\bar{b} = (ab, \quad ab^* + a^*b)$$

The element $\mathcal{E} = (0, 1) \in D$ is called dual unit which has the following properties

$$\mathcal{E} \neq 0, \quad \mathcal{E}^2 = 0, \quad \mathcal{E}1 = 1\mathcal{E} = \mathcal{E}. \quad (1)$$

Let consider the element $\bar{a} \in D$ of the form $\bar{a} = (a, 0)$. Then the mapping $f : D \rightarrow \mathbb{R}$, $f(a, 0) = a$ is an isomorphism. So, we can write $a = (a, 0)$. Then, by the multiplication rule we have that $\bar{a} = a + \mathcal{E}a^*$ and $\bar{a} = a + \mathcal{E}a^*$ is called dual number. The set of dual numbers is given by

$$D = \{\bar{a} = a + \mathcal{E}a^* : a, a^* \in \mathbb{R}, \mathcal{E}^2 = 0\}. \quad (2)$$

which forms a commutative group under addition [2,4].

A Dual function is a function with a dual variable \bar{x} . Then the general expression of a dual function is

$$f(\bar{x}) = f(x + \mathcal{E}x^*) = f(x) + \mathcal{E}x^* f'(x), \quad (3)$$

where $f'(x)$ is derivative of $f(x)$ with respect to x and $x, x^* \in \mathbb{R}$ [3]. Using (3), some well-known functions can be given as follows

$$\begin{cases} \cosh(\bar{x}) = \cosh(x + \mathcal{E}x^*) = \cosh(x) + \mathcal{E}x^* \sinh(x), \\ \sinh(\bar{x}) = \sinh(x + \mathcal{E}x^*) = \sinh(x) + \mathcal{E}x^* \cosh(x), \\ \sqrt{\bar{x}} = \sqrt{x + \mathcal{E}x^*} = \sqrt{x} + \mathcal{E} \frac{x^*}{2\sqrt{x}}, \quad (x > 0). \end{cases} \quad (4)$$

Let $D^3 = D \times D \times D$ be the set of all triples of dual numbers, i.e.,

$$D^3 = \{\tilde{a} = (\bar{a}_1, \bar{a}_2, \bar{a}_3) : \bar{a}_i \in D, i = 1, 2, 3\}. \quad (5)$$

Then the set D^3 is called dual space. The elements of D^3 are called dual vectors. Analogue to the dual numbers, a dual vector \tilde{a} may be expressed in the form $\tilde{a} = \bar{a} + \mathcal{E}\bar{a}^* = (\bar{a}, \bar{a}^*)$, where \bar{a} and \bar{a}^* are the vectors of \mathbb{R}^3 .

Then for any vectors $\tilde{a} = \bar{a} + \mathcal{E}\bar{a}^*$ and $\tilde{b} = \bar{b} + \mathcal{E}\bar{b}^*$ of D^3 , the scalar product and the vector product are defined by

$$\langle \tilde{a}, \tilde{b} \rangle = \langle \bar{a}, \bar{b} \rangle + \mathcal{E}(\langle \bar{a}, \bar{b}^* \rangle + \langle \bar{a}^*, \bar{b} \rangle), \quad (6)$$

and

$$\tilde{a} \times \tilde{b} = \bar{a} \times \bar{b} + \mathcal{E}(\bar{a} \times \bar{b}^* + \bar{a}^* \times \bar{b}), \quad (7)$$

respectively, where $\langle \bar{a}, \bar{b} \rangle$ and $\bar{a} \times \bar{b}$ are the inner product and the vector product of the vectors \bar{a} and \bar{a}^* in \mathbb{R}^3 , respectively.

The norm of a dual vector \tilde{a} is given by

$$\|\tilde{a}\| = \|\vec{a}\| + \varepsilon \frac{\langle \vec{a}, \vec{a}^* \rangle}{\|\vec{a}\|}, \quad (\vec{a} \neq 0). \quad (8)$$

If $\|\tilde{a}\| = 1 + \varepsilon 0$, then \tilde{a} is called dual unit vector. The set of such vectors is defined by

$$\tilde{S}^2 = \{ \tilde{a} = (\vec{a}_1, \vec{a}_2, \vec{a}_3) \in D^3 : \langle \tilde{a}, \tilde{a} \rangle = 1 + \varepsilon 0 \}, \quad (9)$$

and called dual unit sphere [2,4].

The Lorentzian inner product of two dual vectors $\tilde{a} = \vec{a} + \varepsilon \vec{a}^*$, $\tilde{b} = \vec{b} + \varepsilon \vec{b}^* \in D^3$ is defined by

$$\langle \tilde{a}, \tilde{b} \rangle = \langle \vec{a}, \vec{b} \rangle + \varepsilon (\langle \vec{a}, \vec{b}^* \rangle + \langle \vec{a}^*, \vec{b} \rangle),$$

where $\langle \vec{a}, \vec{b} \rangle$ is the Lorentzian inner product of the vectors \vec{a} and \vec{b} in \mathbb{R}_1^3 . Then the Lorentzian character of a dual vector $\tilde{a} = \vec{a} + \varepsilon \vec{a}^*$ is defined as the Lorentzian character of real part \vec{a} , i.e., dual vector \tilde{a} has the same character with real vector \vec{a} [18].

Dual Lorentzian vectors form a space called dual Lorentzian space which is denoted as follows

$$D_1^3 = \{ \tilde{a} = \vec{a} + \varepsilon \vec{a}^* : \vec{a}, \vec{a}^* \in \mathbb{R}_1^3 \}.$$

Let $\tilde{a}, \tilde{b} \in D_1^3$. Then the following product is called dual Lorentzian cross product

$$\tilde{a} \times \tilde{b} = \vec{a} \times \vec{b} + \varepsilon (\vec{a}^* \times \vec{b} + \vec{a} \times \vec{b}^*),$$

where $\vec{a} \times \vec{b}$ denotes the Lorentzian cross product in \mathbb{R}_1^3 .

Let $\tilde{a} = \vec{a} + \varepsilon \vec{a}^* \in D_1^3$. If $\|\tilde{a}\| = -1 + \varepsilon 0$ (resp. $\|\tilde{a}\| = 1 + \varepsilon 0$), then \tilde{a} is called dual unit timelike (resp. spacelike) vector for which followings hold

$$\langle \vec{a}, \vec{a} \rangle = -1 \quad (\text{resp. } \langle \vec{a}, \vec{a} \rangle = 1), \quad \langle \vec{a}, \vec{a}^* \rangle = 0. \quad (10)$$

Then we called the unit sphere consists of all unit dual timelike vectors as dual hyperbolic unit sphere which is represented by \tilde{H}_0^2 ,

$$\tilde{H}_0^2 = \{ \tilde{a} = (\vec{a}_1, \vec{a}_2, \vec{a}_3) \in D_1^3 : \langle \tilde{a}, \tilde{a} \rangle = -1 + \varepsilon 0 \}. \quad (11)$$

Similarly, we called the unit sphere consists of all unit dual spacelike vectors as dual Lorentzian unit sphere which is represented by \tilde{S}_1^2 ,

$$\tilde{S}_1^2 = \{ \tilde{a} = (\vec{a}_1, \vec{a}_2, \vec{a}_3) \in D_1^3 : \langle \tilde{a}, \tilde{a} \rangle = 1 + \varepsilon 0 \}. \quad (12)$$

(See [18]).

Definition 3.1. ([18]) *i) Dual Lorentzian timelike angle:* The dual angle $\bar{\theta} = \theta + \varepsilon \theta^*$ between a dual spacelike vector \tilde{x} and a dual timelike vector \tilde{y} in D_1^3 is defined by $|\langle \tilde{x}, \tilde{y} \rangle| = \|\tilde{x}\| \|\tilde{y}\| \sinh \bar{\theta}$ and called dual Lorentzian timelike angle.

ii) Dual Central angle: The dual angle $\bar{\theta} = \theta + \varepsilon \theta^*$ between dual spacelike vectors \tilde{x} and \tilde{y} in D_1^3 that span a dual timelike vector subspace is defined by $|\langle \tilde{x}, \tilde{y} \rangle| = \|\tilde{x}\| \|\tilde{y}\| \cosh \bar{\theta}$ and called dual central angle.

4. Dual Darboux Frame of a Spacelike Ruled Surface

From E. Study mapping, the lines of the line space IR^3 correspond to dual unit vectors [2,4]. Then, the dual spherical curve lying fully on \tilde{S}^2 represents a ruled surface in IR^3 . In this section, we introduce this correspondence rule for spacelike ruled surfaces and give the dual Darboux frame for these surfaces.

In the Minkowski 3-space IR_1^3 , to determine an oriented spacelike line L it is enough to know a point $p \in L$ and a unit spacelike vector \vec{a} . Then, the moment vector $\vec{a}^* = \vec{p} \times \vec{a}$ can be defined. The moment vector \vec{a}^* does not depend on the chosen of point p . For another point q in L we can write $\vec{q} = \vec{p} + \lambda \vec{a}$ and then $\vec{a}^* = \vec{p} \times \vec{a} = \vec{q} \times \vec{a}$. Reciprocally, when such a pair (\vec{a}, \vec{a}^*) is given, one recovers the spacelike line L as $L = \{(\vec{a} \times \vec{a}^*) + \lambda \vec{a} : \vec{a}, \vec{a}^* \in IR^3, \lambda \in IR\}$, written in parametric equations. The vectors \vec{a} and \vec{a}^* are not independent of one another and they satisfy the following relationships

$$\langle \vec{a}, \vec{a} \rangle = 1, \quad \langle \vec{a}, \vec{a}^* \rangle = 0. \quad (13)$$

The components a_i, a_i^* ($1 \leq i \leq 3$) of the vectors \vec{a} and \vec{a}^* are called the normalized Plucker coordinates of the spacelike line L . From (10), (11) and (13) we see that the dual spacelike unit vector $\tilde{a} = \vec{a} + \varepsilon \vec{a}^*$ corresponds to spacelike line L . This correspondence is known as E. Study Mapping: There exists a one-to-one correspondence between the spacelike vectors of dual Lorentzian unit sphere \tilde{S}_1^2 and the directed spacelike lines of the Minkowski space IR_1^3 [18]. Using this mapping, the study of spatial motion of a spacelike line corresponds to the study of dual Lorentzian spherical curve lying on \tilde{S}_1^2 .

The relations between a ruled surface and dual spherical curves have been introduced by Veldkamp in detailed [21]. Now, we use the similar procedure to introduce the dual Darboux frame of a spacelike ruled surface.

Let (\tilde{k}) be a dual Lorentzian curve on \tilde{S}_1^2 and let the dual position vector of (\tilde{k}) be unit spacelike vector $\tilde{e}(u) = \vec{e}(u) + \varepsilon \vec{e}^*(u)$. The real part \vec{e} draws a curve on S_1^2 and is called the (real) indicatrix of (\tilde{k}) which will be accepted as not a single line in this study. Let consider the parameter u as the arc-length parameter s of the real indicatrix and denote the differentiation with respect to s by primes. Then we have $\langle \vec{e}', \vec{e}' \rangle = -1$. The vector $\vec{e}' = \vec{t}$ is the unit tangent vector of the indicatrix and it is also the unit normal of the surface. The equation $\vec{e}^*(s) = \vec{p}(s) \times \vec{e}(s)$ has infinity of solutions for the function $\vec{p}(s)$. If $\vec{p}_o(s)$ is a solution, then the set of all solutions is given by $\vec{p}(s) = \vec{p}_o(s) + \lambda(s) \vec{e}(s)$, where λ is a real scalar function of s . Therefore we have $\langle \vec{p}', \vec{e}' \rangle = \langle \vec{p}'_o, \vec{e}' \rangle + \lambda$. By taking $\lambda = \lambda_o = -\langle \vec{p}'_o, \vec{e}' \rangle$ we have that $\vec{p}_o(s) + \lambda_o(s) \vec{e}(s) = \vec{c}(s)$ is the unique solution for $\vec{p}(s)$ with $\langle \vec{c}', \vec{e}' \rangle = 0$. Then, the given dual curve (\tilde{k}) corresponding to the spacelike ruled surface

$$\varphi_e = \vec{c}(s) + v \vec{e}(s), \quad (14)$$

may be represented by

$$\tilde{e}(s) = \vec{e} + \varepsilon \vec{c} \times \vec{e}, \quad (15)$$

where

$$\langle \vec{e}, \vec{e} \rangle = 1, \quad \langle \vec{e}', \vec{e}' \rangle = -1, \quad \langle \vec{c}', \vec{e}' \rangle = 0,$$

and \vec{c} is position vector of the striction curve. Then we have

$$\|\tilde{e}'\| = 1 + \varepsilon \det(\vec{c}', \vec{e}, \vec{t}) = 1 + \varepsilon \Delta, \quad (16)$$

where $\Delta = \det(\vec{c}', \vec{e}, \vec{t})$ which characterizes the developable spacelike surface, i.e, the spacelike surface is developable if and only if $\Delta = 0$. Then, the dual arc-length \bar{s} of the dual curve (\vec{k}) is given by

$$\bar{s} = \int_0^s \|\vec{e}'(u)\| du = \int_0^s (1 + \epsilon\Delta) du = s + \epsilon \int_0^s \Delta du . \tag{17}$$

From (17) we have $\bar{s}' = 1 + \epsilon\Delta$. Therefore, the dual unit tangent to the dual curve $\vec{e}(s)$ is given by

$$\frac{d\vec{e}}{d\bar{s}} = \frac{\vec{e}'}{\bar{s}'} = \frac{\vec{e}'}{1 + \epsilon\Delta} = \vec{t} = \vec{t} + \epsilon(\vec{c} \times \vec{t}) . \tag{18}$$

Introducing the dual unit vector $\vec{g} = -\vec{e} \times \vec{t} = \vec{g} + \epsilon\vec{c} \times \vec{g}$ we have the dual frame $\{\vec{e}, \vec{t}, \vec{g}\}$ which is known as dual geodesic trihedron or dual Darboux frame of φ_e (or (\vec{e})). The real parts $\{\vec{e}, \vec{t}, \vec{g}\}$ of dual Darboux frame vectors form an orthonormal frame which is called geodesic trihedron of the indicatrix $\vec{e}(s)$ with the derivations

$$\vec{e}' = \vec{t}, \quad \vec{t}' = \bar{\alpha}\vec{e} + \bar{\beta}\vec{t} + \bar{\gamma}\vec{g}, \quad \vec{g}' = \bar{\gamma}\vec{t} , \tag{19}$$

where $\bar{\gamma}$ is called the conical curvature [6,19].

Let now obtain the dual Darboux formulae of a spacelike ruled surface.

From (18) we have $\langle \vec{t}, \vec{t} \rangle = -1 + \epsilon 0$. Since $\vec{g} = -\vec{e} \times \vec{t}$, we obtain

$$\left\langle \vec{t}, \frac{d\vec{t}}{d\bar{s}} \right\rangle = 0, \quad \frac{d\vec{g}}{d\bar{s}} = -\vec{e} \times \frac{d\vec{t}}{d\bar{s}} . \tag{20}$$

For the derivative of \vec{t} let write

$$\frac{d\vec{t}}{d\bar{s}} = \bar{\alpha}\vec{e} + \bar{\beta}\vec{t} + \bar{\gamma}\vec{g} , \tag{21}$$

where $\bar{\alpha}, \bar{\beta}, \bar{\gamma}$ are the dual functions of dual arc-length \bar{s} . Then from (20) it follows

$$\frac{d\vec{g}}{d\bar{s}} = \bar{\gamma}\vec{t} . \tag{22}$$

Since $\vec{t} = \vec{g} \times \vec{e}$, (22) gives that

$$\frac{d\vec{t}}{d\bar{s}} = \vec{e} + \bar{\gamma}\vec{g} . \tag{23}$$

Then from (18), (22) and (23) we have the following theorem.

Theorem 4.1. *The dual Darboux formulae of a spacelike ruled surface are given by*

$$\frac{d\vec{e}}{d\bar{s}} = \vec{t}, \quad \frac{d\vec{t}}{d\bar{s}} = \vec{e} + \bar{\gamma}\vec{g}, \quad \frac{d\vec{g}}{d\bar{s}} = \bar{\gamma}\vec{t} . \tag{24}$$

From (24), the dual Darboux vector of the trihedron is obtained as $\vec{d} = -\bar{\gamma}\vec{e} + \vec{g}$.

Let now give the invariants of the surface. Since $\bar{s}' = 1 + \epsilon\Delta$, (22) gives that

$$\vec{g}' = \bar{\gamma}(1 + \epsilon\Delta)\vec{t} . \tag{25}$$

From (18) and equality $\vec{g} = \vec{g} + \epsilon\vec{c} \times \vec{g}$, we obtain

$$\begin{aligned}
\tilde{g}' &= \tilde{\gamma}\tilde{t} + \varepsilon(\tilde{c}' \times \tilde{g} \tilde{\gamma} \tilde{c} \times \tilde{t}) \\
&= \tilde{\gamma}\tilde{t} + \varepsilon\tilde{\gamma}(\tilde{c} \times \tilde{t}) + \varepsilon(\tilde{c}' \times \tilde{g}) \\
&= \tilde{\gamma}\tilde{t} + \varepsilon(\tilde{c}' \times \tilde{g}).
\end{aligned} \tag{26}$$

Then (25) and (26) gives us

$$\bar{\gamma}(1 + \varepsilon\Delta)\tilde{t} = \tilde{\gamma}\tilde{t} + \varepsilon(\tilde{c}' \times \tilde{g}), \tag{27}$$

and from (27) we have

$$\bar{\gamma}(1 + \varepsilon\Delta) = \tilde{\gamma} - \varepsilon\delta, \tag{28}$$

where $\delta = \langle \tilde{c}', \tilde{e} \rangle$ and from (28) it follows that

$$\bar{\gamma} = \tilde{\gamma} - \varepsilon(\delta + \lambda\Delta). \tag{29}$$

Moreover, since \tilde{c}' as well as \tilde{e} is perpendicular to \tilde{t} , for the real scalar μ we may write $\tilde{c}' \times \tilde{e} = \mu\tilde{t}$. Then

$$\Delta = \det(\tilde{c}', \tilde{e}, \tilde{t}) = -\langle \tilde{c}' \times \tilde{e}, \tilde{t} \rangle = -\mu \langle \tilde{t}, \tilde{t} \rangle = \mu.$$

Hence $\tilde{e} \times (\tilde{c}' \times \tilde{e}) = \Delta\tilde{e} \times \tilde{t} = -\Delta\tilde{g}$ and $\tilde{c}' = \delta\tilde{e} - \Delta\tilde{g}$.

The functions $\tilde{\gamma}(s)$, $\delta(s)$ and $\Delta(s)$ are the invariants of spacelike ruled surface ϕ_e . They determine the surface uniquely up to its position in the space.

4.1. Elements of Curvature of a Dual Lorentzian Curve

The dual radius of curvature of spacelike ruled surface $\tilde{e}(s)$ is can be calculated analogous to common Lorentzian curve theory as follows

$$\bar{R} = \frac{\left\| \frac{d\tilde{e}}{ds} \right\|^3}{\left\| \frac{d\tilde{e}}{ds} \times \frac{d^2\tilde{e}}{ds^2} \right\|} = \frac{1}{\sqrt{1 + \bar{\gamma}^2}}. \tag{30}$$

The unit Darboux vector \tilde{d}_o is given by

$$\tilde{d}_o = -\frac{\bar{\gamma}}{\sqrt{1 + \bar{\gamma}^2}}\tilde{e} + \frac{1}{\sqrt{1 + \bar{\gamma}^2}}\tilde{g}. \tag{31}$$

It is clear that \tilde{d}_o is spacelike. Then, the dual angle between \tilde{d}_o and \tilde{e} satisfies the followings

$$\sin \bar{\rho} = \frac{1}{\sqrt{1 + \bar{\gamma}^2}} = \bar{R}, \quad \cos \bar{\rho} = \frac{-\bar{\gamma}}{\sqrt{1 + \bar{\gamma}^2}},$$

where $\bar{\rho}$ is the dual spherical radius of curvature.

Furthermore, the corresponding equalities for a dual hyperbolic curve $\tilde{e}_1(\bar{s}_1)$ (timelike ruled surface ϕ_{e_1}) are given as follows:

$$\begin{cases} \bar{s}_1 = \int_0^{s_1} \|\tilde{e}'_1(u_1)\| du_1 = \int_0^{s_1} (1 - \varepsilon \Delta_1) du_1 = s_1 - \varepsilon \int_0^{s_1} \Delta_1 du_1, \quad \Delta_1 = \det(\bar{c}'_1, \bar{e}_1, \bar{t}_1), \\ \delta_1 = \langle \bar{c}'_1, \bar{e}_1 \rangle, \quad \gamma_1 = -\langle \bar{g}'_1, \bar{t}_1 \rangle, \quad \bar{\gamma}_1 = \gamma_1 + \varepsilon(\delta_1 + \gamma_1 \Delta_1) \end{cases} \quad (32)$$

$$\begin{cases} \cosh \bar{\rho}_1 = -\frac{\bar{\gamma}_1}{\sqrt{|1 - \bar{\gamma}_1^2|}}, \quad \sinh \bar{\rho}_1 = -\frac{1}{\sqrt{|1 - \bar{\gamma}_1^2|}}, \quad \text{if } |\bar{\gamma}_1| > 1. \\ \sinh \bar{\rho}_1 = -\frac{\bar{\gamma}_1}{\sqrt{|1 - \bar{\gamma}_1^2|}}, \quad \cosh \bar{\rho}_1 = -\frac{1}{\sqrt{|1 - \bar{\gamma}_1^2|}}, \quad \text{if } |\bar{\gamma}_1| < 1. \end{cases} \quad (33)$$

and

$$\bar{R}_1 = \begin{cases} -\sinh \bar{\rho}_1, & \text{if } |\bar{\gamma}_1| > 1, \\ -\cosh \bar{\rho}_1, & \text{if } |\bar{\gamma}_1| < 1. \end{cases} \quad \text{and} \quad \bar{\gamma} = \begin{cases} \coth \bar{\rho}, & \text{if } |\bar{\gamma}| > 1, \\ \tanh \bar{\rho}, & \text{if } |\bar{\gamma}| < 1. \end{cases} \quad (34)$$

(See [13]).

5. Darboux Approach to Mannheim Offsets of Spacelike Ruled Surfaces

Let φ_e be a spacelike ruled surface generated by dual spacelike unit vector \tilde{e} and φ_{e_1} be a ruled surface generated by dual unit vector \tilde{e}_1 and let the dual Darboux frames of these surfaces be $\{\tilde{e}(\bar{s}), \tilde{t}(\bar{s}), \tilde{g}(\bar{s})\}$ and $\{\tilde{e}_1(\bar{s}_1), \tilde{t}_1(\bar{s}_1), \tilde{g}_1(\bar{s}_1)\}$, respectively. Then φ_e and φ_{e_1} are called Mannheim surface offsets, if

$$\tilde{g}(\bar{s}) = \tilde{t}_1(\bar{s}_1) \quad (35)$$

holds, where \bar{s} and \bar{s}_1 are the dual arc-lengths of φ_e and φ_{e_1} , respectively. This definition gives that φ_{e_1} is a timelike ruled surface, but the generator of this surface can be timelike or spacelike. In this study, we consider the surface φ_{e_1} as a timelike ruled surface with timelike ruling. If the ruling is chosen as spacelike, using Definition 3.1 (ii), similar results can be found. So, in this study we mean that φ_e and φ_{e_1} are spacelike and timelike ruled surfaces, respectively, and for short we don't write the Lorentzian characters of the surfaces hereinafter.

Let now the ruled surfaces φ_e and φ_{e_1} form a Mannheim offset. Then by considering (35), the relationship between the trihedrons of φ_e and φ_{e_1} can be given as follows

$$\begin{pmatrix} \tilde{e}_1 \\ \tilde{t}_1 \\ \tilde{g}_1 \end{pmatrix} = \begin{pmatrix} \sinh \bar{\theta} & \cosh \bar{\theta} & 0 \\ 0 & 0 & 1 \\ \cosh \bar{\theta} & \sinh \bar{\theta} & 0 \end{pmatrix} \begin{pmatrix} \tilde{e} \\ \tilde{t} \\ \tilde{g} \end{pmatrix}, \quad (36)$$

where $\bar{\theta} = \theta + \varepsilon\theta^*$, $(\theta, \theta^* \in \mathbb{R})$ is the dual Lorentzian angle between the dual generators \tilde{e} and \tilde{e}_1 of φ_e and φ_{e_1} . The real angle θ is called the offset angle which is the angle between the rulings \tilde{e} and \tilde{e}_1 , and θ^* is called the offset distance which is measured from the striction point \bar{c} of φ_e to striction point \bar{c}_1 of φ_{e_1} . And from (36) we may write $\bar{c}_1 = \bar{c} + \theta^* \tilde{t}$. Then, $\bar{\theta} = \theta + \varepsilon\theta^*$ is called dual Lorentzian offset angle of the Mannheim ruled surfaces φ_e and φ_{e_1} . If $\theta = 0$, then the Mannheim surface offsets are said to be right offsets.

Now, we give some theorems and results characterizing Mannheim offsets.

Theorem 5.1. Let φ_e and φ_{e_1} form a Mannheim offset. The offset angle θ and the offset distance θ^* are given by

$$\theta = -s + c, \quad \theta^* = -\int_0^s \Delta du + c^*, \quad (37)$$

respectively, where c and c^* are real constants.

Proof. Since φ_e and φ_{e_1} form a Mannheim offset, we can write

$$\tilde{e}_1 = \sinh \bar{\theta} \tilde{e} + \cosh \bar{\theta} \tilde{t}. \quad (38)$$

By differentiating (38) with respect to \bar{s} we have

$$\frac{d\tilde{e}_1}{d\bar{s}} = \cosh \bar{\theta} \left(1 + \frac{d\bar{\theta}}{d\bar{s}}\right) \tilde{e} + \sinh \bar{\theta} \left(1 + \frac{d\bar{\theta}}{d\bar{s}}\right) \tilde{t} + \bar{\gamma} \cosh \bar{\theta} \tilde{g}. \quad (39)$$

From (35) we have that $\frac{d\tilde{e}_1}{d\bar{s}}$ and \tilde{g} are linearly dependent. Then, from (39) we get $\frac{d\bar{\theta}}{d\bar{s}} = -1$ and for the dual constant $\bar{c} = c + \mathcal{E}c^*$ we write

$$\begin{aligned} d\bar{\theta} &= -d\bar{s} \\ \bar{\theta} &= -\bar{s} + \bar{c} \\ \theta + \mathcal{E}\theta^* &= -s - \mathcal{E}s^* + c + \mathcal{E}c^*. \end{aligned}$$

Then from (17) we have

$$\theta = -s + c, \quad \theta^* = -\int_0^s \Delta du + c^*,$$

where c and c^* are real constants.

From (37), the following corollary can be given.

Corollary 5.1. Let φ_e and φ_{e_1} form a Mannheim offset. Then φ_e is developable if and only if offset distance is constant, i.e. $\theta^* = c^* = \text{constant}$.

Theorem 5.2. Let φ_e and φ_{e_1} form a Mannheim offset. Then the relationship between the dual arc-length parameters of φ_e and φ_{e_1} is

$$\frac{d\bar{s}_1}{d\bar{s}} = \bar{\gamma} \cosh \bar{\theta}. \quad (40)$$

Proof. Since φ_e and φ_{e_1} form a Mannheim offset, Theorem 5.1 gives that

$$\frac{d\tilde{e}_1}{d\bar{s}_1} = \tilde{t}_1 = \bar{\gamma} \cosh \bar{\theta} \frac{d\bar{s}}{d\bar{s}_1} \tilde{g}. \quad (41)$$

Then using equality $\tilde{t}_1 = \tilde{g}$, from (41) it follows

$$\bar{\gamma} \cosh \bar{\theta} \frac{d\bar{s}}{d\bar{s}_1} = 1 \quad (42)$$

and from (42) we get (40).

Corollary 5.2. *Let φ_e and φ_{e_1} form a Mannheim offset. Then the relationships between the real arc-length parameters of φ_e and φ_{e_1} are given as follows*

$$\frac{ds_1}{ds} = \gamma \cosh \theta, \quad \frac{ds ds_1^* - ds^* ds_1}{ds^2} = \theta^* \gamma \sinh \theta - (\delta + \gamma \Delta) \cosh \theta. \quad (43)$$

Proof. Since φ_e and φ_{e_1} form a Mannheim offset, (40) holds. By considering (4), the real and dual parts of (40) are

$$\frac{ds_1}{ds} = \gamma \cosh \theta, \quad \frac{ds ds_1^* - ds^* ds_1}{ds^2} = \theta^* \gamma \sinh \theta - (\delta + \gamma \Delta) \cosh \theta, \quad (44)$$

which are desired equalities.

In Corollary 5.1, we give the relationship between the offset distance θ^* and developable spacelike ruled surface φ_e . Now we give the condition for φ_{e_1} to be developable according to θ^* . From (17) and (32) we have

$$ds^* = \Delta ds, \quad ds_1^* = -\Delta_1 ds_1, \quad (45)$$

respectively. Then writing (45) in (44) and using (43) we get

$$\Delta_1 = -\theta^* \tanh \theta + \frac{\delta}{\gamma},$$

and give the following corollaries:

Corollary 5.3. *Let φ_e and φ_{e_1} form a Mannheim offset. Then*

$$\Delta_1 = -\theta^* \tanh \theta + \frac{\delta}{\gamma}, \quad (46)$$

holds.

Corollary 5.4. *Let φ_e and φ_{e_1} form a Mannheim offset. Then φ_{e_1} is developable if and only if $\theta^* = \frac{\delta}{\gamma} \coth \theta$ holds.*

Theorem 5.3. *Let φ_e and φ_{e_1} form a Mannheim offset. There exists the following relationship between the invariants of the surfaces and offset angle θ , offset distance θ^* ,*

$$\delta_1 = \frac{\delta}{\gamma} \tanh \theta - \theta^*. \quad (47)$$

Proof. Let the striction lines of φ_e and φ_{e_1} be $c(s)$ and $c_1(s_1)$, respectively, and let φ_e and φ_{e_1} form a Mannheim offset. Then, from the Mannheim condition we can write

$$\bar{c}_1 = \bar{c} + \theta^* \bar{g}. \quad (48)$$

Differentiating (48) with respect to s_1 we have

$$\frac{d\bar{c}_1}{ds_1} = \left(\frac{d\bar{c}}{ds} + \theta^* \gamma \bar{t} + \frac{d\theta^*}{ds} \bar{g} \right) \frac{ds}{ds_1}. \quad (49)$$

From (32) we know that $\delta_1 = \langle d\bar{c}_1 / ds_1, e_1 \rangle$. Then from (36) and (49) we obtain

$$\delta_1 = \left(\sinh \theta \langle d\bar{c} / ds, \bar{e} \rangle + \cosh \theta \langle d\bar{c} / ds, \bar{t} \rangle + \theta^* \gamma \cosh \langle \bar{t}, \bar{t} \rangle \right) \frac{ds}{ds_1}. \quad (50)$$

Since $\langle d\bar{c} / ds, e \rangle = \delta$, $\langle d\bar{c} / ds, \bar{t} \rangle = 0$, $\langle \bar{t}, \bar{t} \rangle = -1$, from (50) we write

$$\delta_1 = \left(\delta \sinh \theta - \theta^* \gamma \cosh \theta \right) \frac{ds}{ds_1}. \quad (51)$$

Furthermore, from (43) we have

$$\frac{ds}{ds_1} = \frac{1}{\gamma \cosh \theta}. \quad (52)$$

Then substituting (52) in (51) we obtain

$$\delta_1 = \frac{\delta}{\gamma} \tanh \theta - \theta^*.$$

Theorem 5.4. If φ_e and φ_{e_1} form a Mannheim offset, then for conical curvature γ_1 of φ_{e_1} and offset angle θ

$$\gamma_1 = -\tanh \theta, \quad (53)$$

holds.

Proof. From (32) and (36) we have

$$\begin{aligned} \gamma_1 &= -\langle \bar{g}'_1, \bar{t}_1 \rangle \\ &= -\left\langle \frac{d}{ds_1} (\cosh \theta \bar{e} + \sinh \theta \bar{t}), \bar{g} \right\rangle \\ &= -\gamma \sinh \theta \frac{ds}{ds_1}. \end{aligned} \quad (54)$$

From the first equality of (43) and (54), we have $\gamma_1 = -\tanh \theta$.

Theorem 5.5. If the surfaces φ_e and φ_{e_1} form a Mannheim offset, then the dual conical curvature $\bar{\gamma}_1$ of φ_{e_1} is obtained as

$$\bar{\gamma}_1 = -\tanh \bar{\theta}. \quad (55)$$

Proof. From (32), (47), (53) and (54) by direct calculation we have (55).

From (55) we have the following corollary.

Theorem 5.6. *If the surfaces φ_e and φ_{e_1} form a Mannheim offset, then the dual curvature of φ_{e_1} is given by*

$$\bar{R}_1 = \cosh \bar{\theta}. \quad (56)$$

Proof. From (62) we have

$$\sqrt{|1 - \bar{\gamma}_1^2|} = \operatorname{sech} \theta - \varepsilon \theta^* \tanh \theta \operatorname{sech} \theta = \operatorname{sech} \bar{\theta}.$$

Then from (34) we have

$$\begin{aligned} \bar{R}_1 &= \frac{1}{\sqrt{|1 - \bar{\gamma}_1^2|}} = \frac{\operatorname{sech} \theta + \varepsilon \theta^* \tanh \theta \operatorname{sech} \theta}{\operatorname{sech}^2 \theta} \\ &= \cosh \theta + \varepsilon \theta^* \sinh \theta \\ &= \cosh \bar{\theta}. \end{aligned}$$

Then we can give the following corollaries.

Corollary 5.5. *If φ_e and φ_{e_1} form a Mannheim offset and $|\bar{\gamma}_1| < 1$, then the dual spherical radius of curvature of φ_{e_1} is given by*

$$\cosh \bar{\rho}_1 = -\cosh \bar{\theta}. \quad (57)$$

If we assume that $|\bar{\gamma}_1| > 1$, then we have equalities for a timelike ruled surface whose Darboux vector is timelike and the obtained equalities will be analogue to given ones.

6. Conclusions

The dual Darboux frame of a spacelike ruled surface is introduced. Then the characterizations of Mannheim offsets of spacelike ruled surfaces are given in view of dual Darboux frame and new relations between the invariants of Mannheim offsets are obtained. The results of the paper are new characterizations of Mannheim offsets of a spacelike ruled surface and also give the relationships for these offsets to be developable according to offset angle and offset distance. Moreover, the relationship between the developable Mannheim offsets and their striction lines is given.

References

1. Abdel-All N. H., Abdel-Baky R. A., Hamdoon F. M., Ruled surfaces with timelike rulings, *App. Math. Comp.*, 147 (2004) 241–253.
2. Blaschke, W., *Differential Geometrie and Geometrischke Grundlagen ven Einsteins Relativitastheorie* Dover, New York, (1945).
3. Dimentberg, F. M., *The Screw Calculus and its Applications in Mechanics*, (Izdat. Nauka, Moscow, USSR, 1965) English translation: AD680993, Clearinghouse for Federal and Scientific Technical Information.
4. Hacısalihoğlu. H.H., *Hareket Geometrisi ve Kuantemiyonlar Teorisi*, Gazi Üniversitesi Fen-Edb. Fakültesi, (1983).
5. Hoschek, J., Lasser, D., *Fundamentals of computer aided geometric design*, Wellesley, MA:AK Peters, (1993).
6. Karger, A., Novak, J., *Space Kinematics and Lie Groups*, STNL Publishers of Technical Lit., Prague, Czechoslovakia (1978).
7. Küçük, A., Gürsoy O., On the invariants of Bertrand trajectory surface offsets, *App. Math. Comp.*, 151 (2004) 763-773.
8. O'Neill, B., *Semi-Riemannian Geometry with Applications to Relativity*, Academic Press, London, (1983).
9. Orbay, K., Kasap, E., Aydemir, I, Mannheim Offsets of Ruled Surfaces, *Math. Problems in Eng.*, Vol. 2009, Article ID 160917.
10. Önder, M., Uğurlu, H.H., On the Developable Mannheim offsets of timelike ruled surfaces, *Proc. Natl. Acad. Sci., India, Sect. A Phys. Sci.* 84(4) (2014) 541-548.
11. Önder, M., Uğurlu, H.H., Some Results and Characterizations for Mannheim Offsets of the Ruled Surfaces, *Bol. Soc. Paran. Mat.* 34(1) (2016) 85–98.
12. Önder, M., Uğurlu, H.H., On the Invariants of Mannheim Offsets of Timelike Ruled Surfaces with Spacelike Rulings, *Asian-European Journal of Math.* 8(1) (2015) 1550009.
13. Önder, M., Uğurlu, H.H., Dual Darboux Frame of a Timelike Ruled Surface and Darboux Approach to Mannheim Offsets of Timelike Ruled Surfaces, *Proc. Natl. Acad. Sci., India, Sect. A Phys. Sci.* (2013) 83:163-169.
14. Önder, M., Uğurlu, H.H., On the Developable Mannheim offsets of spacelike ruled surfaces, *arXiv:0906.4660v5 [math.DG]*.
15. Papaioannou, S.G., Kiritsis, D., An application of Bertrand curves and surfaces to CAD/CAM, *Comp. Aided Design*, 17(8) (1985) 348-352.
16. Pottmann, H., Lü, W., Ravani, B., Rational ruled surfaces and their offsets, *Graph. Models and Image Process*, 58(6) (1996) 544-552.
17. Ravani, B., Ku, T. S., Bertrand Offsets of ruled and developable surfaces, *Comp. Aided Geom. Design*, 23 (2) (1991) 145-152.
18. Uğurlu, H.H., Çalışkan, A., The Study Mapping for Directed Spacelike and Timelike Lines in Minkowski 3-Space IR_1^3 , *Math. and Comp. Appl.*, 1(2) (1996) 142-148.
19. Uğurlu, H.H., Önder, M., On Frenet Frames and Frenet Invariants of Skew Spacelike Ruled Surfaces in Minkowski 3-space, VII. Geometry Symposium, 07-10 July 2009, Kırşehir, Turkey.
20. Uğurlu, H.H., The relations among instantaneous velocities of trihedrons depending on a spacelike ruled surface, *Hadronic Journal*, 22 (1999) 145-155.
21. Veldkamp, G.R., On the use of dual numbers, vectors and matrices in instantaneous spatial kinematics, *Mech. Mach. Theory*, II (1976) 141-156.
22. Wang, F., Liu, H., Mannheim partner curves in 3-Euclidean space, *Math. in Practice and Theory*, 37 (1) (2007) 141-143.



NATURAL SCIENCE & DISCOVERY

ISSN: 2149-6307

Lycia Press LONDON UK



International Journal of
Natural Science and Discovery
Open Access Scientific Journal
March 2015, Vol.1, No.1

www.natscidiscovery.com