BIOTECHNOLOGY OF VITAMINS, PIGMENTS AND GROWTH FACTORS

Edited by

ERICK J. VANDAMME

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PREFACE

Vitamins and related growth factors belong to the few chemicals with a positive appeal to most people; the name evokes health, vitality, fitness, strength. . . . each one of us indeed needs his daily intake of vitamins, which should normally be provided via a balanced and varied diet. However, current food habits or preferences, or food processing and preservation methods do not always assure a sufficient natural daily vitamin supply, even for a healthy human being; this is all the more true for stressed or sick individuals. Although modern society is seldom confronted with the notorious avitaminoses of the past, they do still occur frequently in overpopulated and poverty- and famine-struck regions in many parts of the world. Apart from their in-vivo nutritional–physiological roles as growth factors for man, animals, plants and micro-organisms, vitamin compounds are now being introduced increasingly as food/feed additives, as medical–therapeutical agents, as health-aids, and also as technical aids. Indeed, today an impressive number of processed foods, feeds, cosmetics, pharmaceuticals and chemicals contain extra added vitamins or vitamin-related compounds, and single or multivitamin preparations are commonly taken or prescribed.

These reflections do indicate that there is an extra need for vitamin supply, other than that provided from plant and animal food resources. Most added vitamins are indeed now prepared chemically and/or biotechnologically via fermentation/bioconversion processes.

Similarly, other related growth factors, provitamins, vitamin-like compounds, i.e. special unsaturated fatty acids, gibberellins and certain pigments—some of which are increasingly used in agriculture, food/feed production or processing and as health aids—are equally important biotechnological products, where production via microbial fermentation or micro-algal bioconversion is now applied industrially. Indeed, biotechnology—based on bacteria, yeasts, fungi and micro-algae—here again has been very instrumental in procuring sufficient amounts of several of these valuable complex molecules via natural processes, although for certain products there is fierce competition with chemical synthesis. Abundant and excellent literature is available on the chemical properties, biochemistry, nutritional aspects and clinical aspects of vitamins and related products, while that on microbial synthesis and production methods is rather scarce or difficult to find.

In this respect, this book intends to assemble useful information on the (potential) industrial synthesis of economically important vitamins, growth factors and pigments, with emphasis on biotechnological aspects including microbiology, genetics, biochemistry and bioprocess technology; so far, such information is scattered widely in the scientific literature: for some products, only secrecy and sparse data are available, other excellent volumes deal with only one specific vitamin compound, while others then stress the chemical synthesis processes. Therefore, I felt that there was a scientific need for a biotechnological survey of the world of vitamins and related compounds synthesis.

The help of several colleagues and friends in suggesting potential authors for difficult-to-get chapters has been invaluable in constructing a rather comprehensive volume; so was the positive interaction with all my contributors. In this respect, I am particularly indebted to:
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I suspect that my wife, Mireille, could only have withstood my 'mental absence', strengthened with multivitamin preparations, although my sole vitamin-shot was her encouraging and moral support during this biotechnological enterprise.

E. J. Vandamme

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VITAMINS AND RELATED COMPOUNDS VIA MICRO-ORGANISMS: A BIOTECHNOLOGICAL VIEW

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1 HISTORICAL

The start of the history of vitamins can be traced back to 400 BC, when Hippocrates reported that eating liver could cure night-blindness. Much later, in the 16th century, the therapeutical effects of lemon juice against scurvy or scorbut became known; scorbut had *inter alia* caused the loss of 100 crew members on Vasco da Gama's journey around Cape Hope. The English ship doctor James Lind studied this disease further and described in 1757 in his book *A Treatise of Scurvy* the beneficial effect of eating fresh vegetables and fruits in preventing it. For another nutritional deficiency disease (already mentioned in 1762 by Oviedo), the Italian doctor Francesco Frapoli used the name pellagra (pella = skin; agra = rough). In the 19th century in Japan, the Hikan child disease (keratomalacia and xerophthalmia) was successfully treated by including ale-fat, cod liver oil or chicken liver in the diet. Trousseau discovered that cod liver oil and also, direct sunlight, had a curing effect on rickets, a disease already well described by Whistler in 1645. In the Far-East, when hulled rice was replaced by dehulled or polished rice, a sharp increase in the occurrence of beriberi was observed. In 1897 Eijkman observed that poultry fed with polished rice developed polyneuritis, a disease very similar to human beriberi. This disease could also be prevented and cured by feeding rice and the silver fleece of the rice kernel. Grijns in 1901 hypothesised that beriberi was caused by a protecting factor, which was obviously lacking in dehulled rice. We now know that all these diseases are a result of nutritional vitamin deficiencies (Machlin, 1984).

Around 1910, Hopkins in the UK and Osborne & Mendel in the USA initiated modern vitamin research and developed a theory, stating that diseases such as scurvy, pellagra, rickets, beriberi, etc., are the result of a lack of certain essential food components. The Polish chemist Casimur Funk isolated in 1912 from rice bran a beriberi-preventing compound, displaying chemical properties of an amine; this led him in 1912 to coin the name vitamin for this type of compounds.

In 1913, McCollum & Davis demonstrated a liposoluble factor A in butter fat and egg yolk, and in 1915, a water-soluble factor B was found in wheat-germ. It was Drummond in 1920 who named the fat-soluble factor, vitamin A; the water-soluble anti-beriberi factor was named vitamin B; the water-soluble anti-scorbut factor vitamin C. In 1925, the fat-soluble anti-rickets factor was named vitamin D. After 1930, discovery and isolation of several other vitamins followed quickly and their structure, nutritional and chemical properties and synthesis were studied in great detail in the following decades.

These aspects of vitamins and growth factors are compiled in several excellent standard references (Goodwin, 1963; Sebrell & Harris, 1971; De Luca, 1978; Machlin, 1984; De Leenheer *et al.*, 1985; Diplock, 1985; Chytil & McCormick, 1986; Adrian, 1988; Friedrich, 1988).

2 VITAMINS: WHAT'S IN A NAME?

Vitamin nomenclature was initially based on the use of letter symbols, alphabetically arranged to time of discovery. Soon, it appeared that one-letter named vitamins were multiple complexes, and this led to the addition of an index to the original letters (B_1, B_2, . . .). Often, when the function of the vitamin became known, an appropriate letter symbol was chosen, i.e. vitamin K, with K as the first letter of the German word *Koagulation*; other names reflected deficiencies, i.e. aneurin (B_1) for anti-polyneuritis vitamin; vitamin PP = "pellagra-preventing" vitamin. Letter names or trivial names are generally more in use rather than the IUPAC names. The division into fat- and water-soluble vitamins as introduced by McCollum & Davis, is still universally applied.

A listing of well-recognised vitamin compounds is presented in Table 1.

From a chemical point of view, vitamins are a very heterogeneous mixture of compounds, yet they can be considered as a single group, since they are all organic compounds which are essential for a healthy development of humans and animals and need to be present in their food, since their body is not able at all—or not sufficiently able—to synthesize them. Indeed, certain vitamins can be formed partially or indirectly in the body:

(a) compounds—often called provitamins—with no apparent vitamin activity can be converted within the body into a vitamin, i.e.
β-carotene (in vegetables, fruits) $\longrightarrow$ vitamin A
tryptophan (in protein-rich food) $\longrightarrow$ nicotinic acid (niacin)
7-dehydrocholesterol (in skin) $\xrightarrow[UV]{}$ vitamin D_3 (cholecalcifenol)

(b) other vitamin compounds are formed by the intestinal bacterial flora i.e. vitamin K, some B-vitamins, i.e. B_{12}, etc.

Most vitamin compounds thus have to be provided via daily food/feed intake

Table 1
Survey of Vitamins and Growth Factors

Vitamin group	*Important examples*	*Important natural sources*	*International Units (IU)*	*Recommended adult daily intake*
Provitamin A group	β-carotene, γ-carotene, α-carotene, kryptoxanthine	Vegetables, fruits	1 IU = 0·6 μg carotene; 1 μg = 3·34 IU	2·4 mg β-carotene
Vitamin A group	Retinol (vitamin A_1), 3-dehydroretinol (vitamin A_2), retinal (vitamin A_1-aldehyde)	Fish oil, liver, milk and daily products, eggs	1 IU = 0·30 μg retinol	0·75 mg retinol
Provitamin D	7-Dehydrocholesterol, ergosterol	Yeast		
Vitamin D group	Ergocalciferol (D_2), cholecalciferol (D_3)	Fish oil, liver, egg yolk, milk, dairy products	1 IU = 0·025 μg vitamin D_3; 1 μg = 40 IU	
Vitamin E group	α-Tocoferol, β-tocoferol, γ-tocoferol, δ-tocoferol	Plant oils, vegetables liver, eggs, dairy products	1 IU = 1·0 mg *dl*-tocoferol-acetate	2·5 μg vitamin D_3 30 mg
Vitamin F group (polyunsaturated fatty acids, PUFAs), ω-3-fatty acids)	Linolic acid, γ-linolenic acid, eicosa-pentaenoic acid (EPA), DHA	Fish oil, algae, fungi	—	—
Vitamin K group	Phylloquinone (K_1) or phytomenadion, phamoquinone (K_2) or menaquinone, menadion (K_3), menadiol (K_4)	Liver, vegetables bacterial flora, plant oils	—	0·1 mg
Vitamin B_1	Thiamine	Cereals, liver, meat, vegetables, dairy products, yeast	1 IU = 3 μg thiamine; 1 μg = 0·333 IU	0·8–1·6 mg
Vitamin B_2 (vitamin G)	Riboflavin	Liver, eggs, dairy products, vegetables, meat, bacterial flora	—	1·2–1·3 mg
Vitamin PP (vitamin B_3)	Nicotinamide, nicotinic acid (niacin)	Liver, cereals, meat, potatoes, vegetables, yeast, trypto-phane-protein		10–15 mg
Pantothenic acid (vitamin B_5)	Pantothenic acid, coenzyme A	Liver, eggs, molasses vegetables, cereals	—	10–20 mg
Vitamin B_6 group	Pyridoxine (pyridoxol), pyridoxal pyridoxamine	Liver, potato, vegetables, meat, yeast	—	2 mg
Biotin (vitamin H, B_8)	Biotin	Liver, egg yolk, vegetables, cane molasses bacterial flora		0·3 mg

(continued)

Table 1—*contd.*

Vitamin group	*Important examples*	*Important natural sources*	*International Units (IU)*	*Recommended adult daily intake*
Folic acid (B_9-group, B_c, M)	Pteroyl-glutamic acid, pteroyl-diglutamic acid, pteroyl-triglutamic acid	Cereals, liver, meat, milk, vegetables	—	400 μg
Vitamin B_{12} group	Cyanobalamin (B_{12}), hydroxycobalamin (B_{12b}), nitrosocobalamin (B_{12c})	Meat, liver, milk, bacterial flora	—	2 μg
Vitamin B_{13}	Orotic acid			
Vitamin C group	Ascorbic acid (vitamin C), dehydro-ascorbic acid	Citrus fruit, fruit, vegetables, potato	1 IU = 50 μg L-ascorbic acid	50 μg (not for animals except, primates, cavia, etc.)
Lipoic acid		Yeast, meat		
Inositol		Yeast, meat, vegetables		
Choline (B_7, J)		Egg yolk, meat, hops		50–600 mg
Para-aminobenzoic acid (PABA) (B_x, H', H_2)		Yeast		
Gibberellins		Plants, fungi		—

The vitamin content was originally and still often is expressed in International units (IU), which relate to the biological activity of a certain amount of pure vitamin towards a specific test animal.

Presently, it is common practice to express the vitamin content as mg or μg per 100 g of material; conversion factors for IU values into weight units are also given in Table 1. Recommended daily intake per person per day (FAO/WHO data) is also given.

Quantitative assays for vitamin content, in foodstuffs, concentrated mixtures, synthetic formulations, tissues, blood, fermentation broths, etc., are very important and ever more sophisticated techniques (e.g. HPLC) are introduced; for several vitamins, i.e. B_{12}, biotin, etc., a microbiological bioassay is still the method of choice (Freed, 1966; Berg & Behagel, 1972; De Leenheer *et al.*, 1985).

3 PHYSIOLOGICAL FUNCTIONS

Vitamins have a catalytic role in the body in enabling optimal synthesis, conversion and degradation of macromolecules such as nucleic acids, proteins, lipids and carbohydrates.

The biochemical (physiological) function of most water-soluble vitamins is well known: they are part of co-enzymes and thus co-responsible for specific biochemical reactions (Machlin, 1984; Diplock, 1985). A survey is given in

Table 2
Water-Soluble Vitamins and their Corresponding Coenzymes

Vitamin	*Coenzyme*	*Group Transfer*
Nicotinamide (B_3 or PP)	Nicotinamide-adenine dinucleotide (NAD+)	Hydrogen
	Nicotinamide-adenine dinucleotide phosphate (NADP+)	Hydrogen
Riboflavin (B_2)	Flavine adenine mononucleotide (FMN)	Hydrogen
	Flavine adenine dinucleotide (FAD)	Hydrogen
Pyridoxine (B_6)	Pyridoxalphosphate (PLP)	Amino-group, decarboxylation
Folic acid (B_9)	Tetrahydrofolic acid	Formyl
Biotin (H)	Biotin (biocytin, *ε-N*-biotinyllysine)	Carboxyl
Pantothenic acid (B_5)	Coenzyme A	Acyl
Thiamine (B_1)	Thiaminepyrophosphate (TPP)	C_2-aldehyde, decarboxylation
Cyanocobalamin (B_{12})	B_{12}-coenzyme	Carboxyl

As to the function of fat-soluble vitamins and vitamin C, much controversy still exists; their involvement can often be traced down to specific biochemical processes (Table 3), although their exact function is not yet known in all cases (De Luca, 1978; Diplock, 1985).

Much debate also exists about the positive effects of high (mega) doses of certain vitamins, (e.g. vitamin C) on human and animal physiology; on the other hand, several hypervitaminoses, (e.g. A, D, K) are well known (Machlin, 1984).

Some vitamins display different activity toward man or animal, i.e. ergocalciferol (D_2) is poorly active in poultry, while in other animals and man it is equally active as cholecalciferol (D_3). This observation has great practical repercussions on feed formulations. Others are essential solely for man, (i.e. vitamin C), while most animals (except primates, cavias) can synthesise them.

Compounds which specifically counteract the functioning of vitamins are also known and are named antivitamins or vitamin antagonists (Machlin, 1984). Their negative action can be based on degradation of the vitamin (thiaminase, ascorbase, etc.), or on the complexation of the vitamin into a non-resorbable complex, (i.e. avidin plus biotin). N5-Hydroxy-L-arginine is a vitamin B_{12} antagonist (Perlman *et al.*, 1974). Dicoumarin excludes vitamin K from the prothrombin synthesis system and amethopterin is an antagonist of folic acid; however, both antivitamins are medically important for the treatment of

Table 3
Important Biochemical Actions of Fat-Soluble Vitamins and of Vitamin C

Vitamin	*Physiological functions*
Vitamin A active form: 11-*cis*-retinol	Retinol is part of rhodopsin, the light sensitive molecule in the eye; Biosynthesis of mucopolysaccharides; synthesis and maintenance of epithelial cells
Vitamin D_3 (cholecalciferol) active form: 1, 25-diOH-cholecalciferol	Regulation in Ca^{2+} and phosphorous metabolism
Vitamin E: (α-tocoferol)	Antioxidant action towards unsaturated compounds, i.e. fatty acids, etc.; membrane integrity
Vitamin K_1: (phylloquinone)	Essential for formation of prothrombine, a blood coagulation factor; Cofactor for carboxylation of protein bound glutamate residues to form γ-carboxyglutamates
Vitamin C	Cosubstrate of monooxygenases; Role in redox reactions and in hydroxylation reactions of amino acids and amines (i.e. proline conversion into hydroxyproline in collagene); Role in hormone-synthesis, iron absorption, etc.

thrombosis and leukemia, respectively. Antivitamins present in our daily food are usually destroyed during processing or cooking.

Excellent information on detailed nutritional, clinical and physiological aspects of vitamins has been assembled by Machlin (1984), Diplock (1985) and Friedrich (1988).

4 TECHNICAL FUNCTION OF VITAMINS, PIGMENTS AND GROWTH FACTORS

In addition to their nutritional, physiological and medical importance, vitamins and vitamin-like compounds have also found large-scale technical applications as antioxidants (vitamin C, E), as acidulant (vitamin C), and as pigments (β-carotene and analogues) in the food, feed, cosmetic, chemical and pharmaceutical industry (Machlin, 1984; Diplock, 1985; Florent, 1986).

Apart from the synthetic pigments, most of the natural colorants are now being extracted from plants and animals, e.g. annatto, grapes, red beets, paprika, female insects (*Coccus cacti*). Micro-organisms could be an excellent source of non-toxic food colorants, but except for the fungal *Monascus* pigments (monascin), used in the Orient, and for astaxanthin from yeast few attempts have been made to produce and introduce them (Lin, 1973;

Palleroni *et al.*, 1978; Institute of Food Technologists, 1980; Wong & Koehler, 1981). Indeed, in addition to the well-known provitamin-carotenoids, a range of anthraquinone pigments, chlorophylls and several others have been demonstrated in bacteria, yeasts, fungi and algae and are attractive as natural colorant.

In this respect, more emphasis should be given to screening and research on other natural pigment synthesis via safe micro-organisms; this would open up a wider application area in agriculture, food, feed, chemicals, cosmetics and pharmaceuticals.

Fungal gibberellins are already widely used as plant growth-regulators in agriculture and horticulture and in the brewing industry (Jefferys, 1970; Palmer, 1974; Brueckner *et al.*, this volume).

Details about technical applications of certain vitamins, pigments and gibberellins are given in the corresponding chapters in this volume.

5 PRODUCTION AND APPLICATION

The staple food of man, including cereals, rice, potato, vegetables, fruits, milk, fish, meat, eggs, forms his basic source of vitamins and growth factors. Adequate nutrition should thus supply this daily vitamin need, which however increases with physical exercise, pregnancy, lactation, active growth, reconvalescence, drug abuse, stress, air pollution, etc. Pathological situations (intestinal malresorption, stressed intestinal flora, liver/gall diseases, drug, antibiotic or hormone treatment, enzyme deficiencies), can also lead to vitamin shortages despite a sufficient intake. Malnourishment in many countries of the world also asks for direct medical remediations, combined with diet adjustment. Vitamin-enriched and medicated feed is used worldwide to procure healthy livestock.

However, derived concentrates or extracts from these vitamin-rich natural food products find relatively little use in the food, feed, pharmaceutical or cosmetic industry (except for ω-3-fatty acids, vitamin E, etc.). Some of the reasons are:

(a) the average daily intake of vitamins does not always seem to be supplied solely via these natural products;
(b) the level of the natural plant/animal source vitamins is usually relatively low and fluctuates drastically;
(c) their organoleptic presentation and shelf-life is often far from optimal;
(d) vitamins are labile molecules during the process of preservation, storage or preparation of foodstuffs and are generally very sensitive to pH, heat, light, oxygen, etc.; water-soluble vitamins are easily lost by aqueous extraction or manipulation of foods.

These factors have led to the industrial manufacturing of most vitamins and growth factors. Current world production of important vitamins is given in Table 4.

At the moment, several vitamins are produced only or mainly chemically

Table 4
Survey of Vitamins and Growth Factors—Production and Application

Vitamin group (see also Table 1)	*Industrial production (E = extraction; C = chemical synthesis; B = biotechnology)*	*Application (F = food/feed; M = medical; T = technical)*	*World production*		
			tons/year	*Average price ($/kg) (1988)*	*Producer company or country*[a]
Provitamin A group	E C B (fermentation, algal)	F M T	100	450	2, 5, 6, 6a, 15a, 18, 20, 22, 25
Vitamin A group	C	F M	2500	70	33, 34, 44, 46
Provitamin D	C B (fermentation)	F M			8, 14a, 18, 34
Vitamin D group	C B (fermentation)	F M	25	350	
Vitamin E group	E C B (algal)	F M T	6800	17	9, 11, 17, 18, 33, 34
Vitamin F group	C E B (fermentation, algal)	F M	200, 2000 (GLA) (EPA, DHA)	800, 50 (GLA) (EPA, DHA)	3, 6, 6a, 10, 18, 26, 32, 35, 37, 38
Vitamin K group	C	M	1·3	1500	9, 11, 17, 18, 34, 45
Vitamin B_1	C	F M	2000	23	2, 18, 31, 39, 40, 41
Vitamin B_2	C B (fermentation)	F M	2000	27	2, 5, 13, 18, 24, 30, 41
Vitamin PP (vitamin B_3)	C	F M	8500	4	2, 7, 18 47
Pantothenic acid (vitamin B_5)	C B (fermentation)	F M	4000	4	6a, 18, 39, 41
Vitamin B_6 group	C B (fermentation)	F M	1600	25	18, 31, 39, 41
Biotin (vitamin H, B_8)	C (B)	F M	3	5000	2, 18, 24, 27, 39, 43
Folic acid (B_9)	C	F M	300	115	18, 39, 41, 42, 48
Vitamin B_{12} group	B (fermentation)	F M	5–10	5000	14, 15, 16, 21, 23, 24, 26, 33, 36

(continued)