Chapter

Plant Sources of Vitamin D and Its Medicinal Application in Sub-Sahara Africa

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Abstract

Vitamin D is one of the fat-soluble vitamins structurally derived from cholesterol and similar to the reproductive hormones by possessing the ABCD hexagonal rings. Its open seco-B triene B ring along with the possession of 1,25 dihydroxycholesterol side chain has been postulated as possible configuration allowing for its flexibility to interact with many tissues including bones causing myriads of biological effects that are medicinally beneficial. Aside from the established role of vitamin D in bone and mineral metabolic diseases, exploiting this property of the vitamin had been in practice in orthodox medical practice and even in traditional sub-Sahara method of managing many disease conditions.

Keywords: plant sources of vitamin D, medicinal application, bone and mineral metabolism

1. Introduction

1.1 Preamble

"Africa and by extension her sub-Sahara regions are noted for various folklores some of which center on application of various traditional methods and means in solving many problems including medical issues. It is thus a common saying in Africa that 'before the advent of tooth brush and paste, Africans have their own mouth cleaning devises".

2. Definitions

2.1 Vitamins

Vitamins are organic compounds essential in small quantities for normal physiologic and metabolic functioning of the body [1]. Vitamins are a large family usually grouped as micronutrients; they are mostly derived from diets with few exceptions and unlike other food substances, this family of micronutrients usually exist in complexes with one another and thus cannot be obtained from a single dietary source.

Functionally, vitamins are involved in various metabolic processes where they serve usually as coenzymes in various biochemical reactions associated with proper functioning of the whole organism [2]. They thus catalyze organic reactions by participating in the formation of hormones, cells, chemical structures of the nervous system, composition of genetic material and a host of other biological processes. They also combine with proteins to form enzymes which participate in various body reactions including in the development of body's immune system.

Probably because vitamins are present in small quantities, in the past, diseases of vitamin deficiencies were treated using various vitamins supplementarily in their management; however, advancement in science has led to many biochemical and biological methods that are appropriately used in the identification, measurement and diagnosis of diseases associated with many of the known vitamins.

Due to the involvement of these vitamins in several metabolic processes in spite of their small quantities, their deficiencies usually manifest clinically in various forms; for example, pellagra and beriberi are clinical conditions associated with the deficiency of niacin and thiamine respectively, (sub-groups of vitamin B), scurvy is a clinical condition associated with vitamin C deficiency, while osteomalacia (in adults) and rickets (in growing children) are associated with vitamin D deficiencies. Night blindness is associated with vitamin A deficiency, deficiency of vitamin B12 or that of folic acid is associated with megaloblastic anemia while spinal bifida has been associated with the deficiency of folic acid in the mother while the baby was in-utero [2]. Because vitamins as essential nutrients are mostly derived from diets, etiology of hypovitaminosis has always been associated with either in-adequate intake from diet or abnormality of absorption whereby a large quantity of these essential nutrients remains unabsorbed even when present abundantly in diet. Generally, vitamin toxicity is associated with the fat-soluble series because of their insolubility in the aqueous medium which largely constitutes the human system; however, excessive ingestion of vitamin A has been known to result in toxic manifestations which may ultimately result in liver damage [2].

2.2 Classification of vitamins

Vitamins are generally classified based on their solubility in aqueous or lipid medium. Thus, there are the fat-soluble vitamins (A, D, E and K) and the water-soluble ones (vitamins B complex and C). Although they are usually classified into these two broad groups, the classification is for convenience based on the chemical structure of vitamins; most of the vitamins have sub-groups that are no less prominent in name as the known main group. For example, while vitamin A is available either as the plant (carotenoid) or animal (retinol) types, vitamin B has several sub groups which have been distinctly classified based on structure and function. On the other hand, the name vitamin E, which is a known fat-soluble vitamin, refers to a family of eight naturally occurring homologs that are synthesized by plants from homogentisic acid. They are all derivatives of 6-chromanol and differ in the number and position of methyl groups on the ring structure. Also, vitamin D is another classical example of a lipid-soluble vitamin. The name, vitamin D, refers to about 5 different compounds generally classified as such, these are: 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3, 24,25-dihydroxyvitamin D3 (24R,25-(OH)2D3, 1,25-dihydroxyvitamin D2 (1,25-(OH2)D), 25-hydroxyvitamin D3 (25-OH-D3), 25-hydroxyvitamin D2 (25-OH-D2). Hence, the general classification of vitamins notwithstanding, several sub-groups of vitamins exist which when considered based on structure, function and activity will make the conventional broad classification of vitamins too simplistic in terms of their overall relevance in human metabolic processes. The focus of this chapter is however on vitamin D with particular emphasis on its plant sources and medicinal applications in sub-Sahara Africa.

3. Vitamin D

Vitamin D is one of the fat-soluble vitamins that has distinct biochemical functions in human metabolism. It exists in five active forms

i. 1,25-dihydroxyvitamin D3(1,25-(OH)2D3,

ii. 24,25-dihydroxyvitamin D3(24R,25-(OH)2D3

iii. 1,25-dihydroxyvitamin D2(1,25-(OH2)D)

iv. 25-hydroxyvitamin D3(25-OH-D3)

v. 25-hydroxyvitamin D2(25-OH-D2)

3.1 Sources and production of vitamin D

The general conception is that vitamin D is synthesized only in the body, however, evidences abound that vitamin D is available in different forms in some plants and fruits in sub-Sahara Africa. There are also reports on application of these plant sources in the treatment of some vitamin D related diseases. Vitamin D2 (ergosterol) has been identified in some plants and fungi. Vitamin D2 differs from D3 in having a double bond between C22 and C23 and a methyl group at C24 in the side chain. D2 can be considered the first vitamin D analog which is converted to D3 by ultraviolet radiation. As earlier stated, plants like perennial ryegrass contain some amounts of ergosterol which when ingested can also be readily converted to D3 in the body [3].

Vitamin D3 has many dietary sources. The parent compound (D2) is derived essentially from dietary sources like egg yolk, sea fatty fish, liver, and mushroom among others. The production of vitamin D3 (D3) in the skin is not an enzymatic process. Sea fatty fish essentially contain vitamin D2.

3.2 Plant sources of vitamin D

Accidental discovery of activation of some vegetables and crops by exposure to mercury lamp led to the identification of vitamin D2 in some inert foods like cottonseed, wheat and lettuce [4]. Later, vitamin D2 was identified from solutions of ergosterol irradiated with UV light in-vitro [5]. Hence, contamination of plants with fungi which has a high concentration of ergosterol led to the discovery of "plants contaminated with fungi" as veritable source of vitamin D2. This initial concept on the presence of vitamin D in plants however changed with the discovery of a type of calcium intoxication in grazing animals similar to that caused by vitamin D toxicity that consumed certain plants [6]. This was believed to be due to vitamin D3 or a metabolite of vitamin D3 present in the plants that stimulate calcium absorption producing hypercalcemia and deposition of calcium in soft tissue including aorta, heart, kidneys, intestines, and uterus [6].

Hence, while plants like *Solanum glaucophyllum* Desf. (*S. glaucophyllum*), *Cestrum diurnum* L. (*C. diurnum*) and *Trisetum flavescens* Beauv. (*T. flavescens*) were found to cause calcium intoxication similar to that caused by vitamin D toxicity in grazing animals, rats and even chickens in South America [7–9]; similar effects of plants ameliorating calcium intoxication were found in studies on chicken in Africa and her sub-Sahara using *Moringa oleifera* leaves [10]. Aside from above, provitamin D3 and vitamin D2 (7-dehydro cholesterol) have been identified in leaves of plants like the genus *Solanaceae* and in *S. lycopersicum*, *S. glaucophyllum* and *C. annuum* amongst others [11–15].

Like most plant and herbal preparations, there are lots of knowledge gap in the biochemical and physiological mechanism behind application of these plant materials as sources of nutrients and most importantly in the management of diseases. However, isolation and characterization of vitamin-like substances in some of the plant may allow for the assumption of most of the claimed empirical roles of these plants and herbal preparations (WHO, 2002) [16].

Ocimum gratissimum (**Figure 1**) is one of the plants commonly used (empirically) to treat open wounds in rural setting of sub-Sahara Africa. The phytochemical analysis of this plant is well documented [17]. The assumed theory is that at higher temperatures, leaves of this plant facilitate collagen and fiber formation on the open wound thus enhancing clotting and angiogenesis [18]. However, the direct effect traceable to vitamin D content and activity remain to be elucidated.

3.3 Chemistry and biochemistry of vitamin D

Structurally, vitamin D is derived from cholesterol, and it is related to the classical steroid hormones with their traditional A B C D hexagonal rings. However, its uniqueness is derived by its possession of both 1,25-dihydroxycholesterol side chain and a seco-B triene structure. This lack of a complete B-ring as in steroids thus allows for the molecule to be depicted in a non-steroidal, extended formation in contrast to a classical steroid hormonal configuration which may or may not possess a truncated side chain but all have fully in-tact A B C D steroid rings (**Figure 2**). Biochemical evidences have shown that these structural differences allow for

Figure 1.
Ocimum gratissimum also known as clove basil, African basil, and in Hawaii as wild basil.

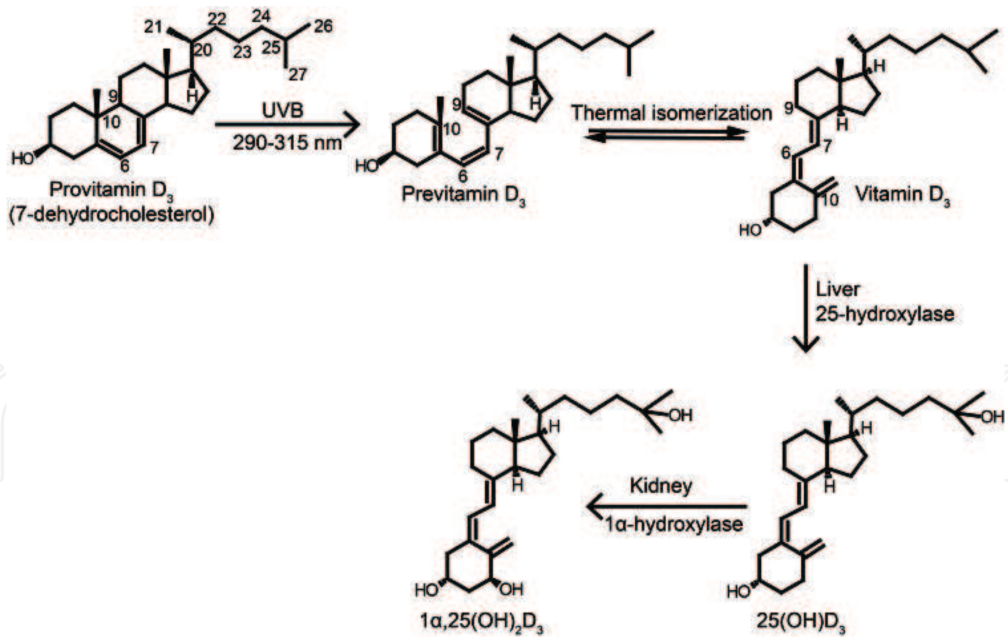

Figure 2.
Synthesis and activation of vitamin D. Vitamin D^3 is synthesized in the skin upon UVB exposure. The UVB exposure of provitamin D^3 (7-dehydro cholesterol) in the skin breaks the B-ring to form previtamin D^3, which undergoes thermally induced rearrangement to vitamin D^3. Vitamin D^3 is transported to the liver where it is hydroxylated at C-25 by the enzyme 25-hydroxylase producing 25OHD^3, which is the major circulating form in vertebrates. The 25OHD^3 is hydroxylated a second time at C-1 in the kidneys to the active metabolite 1,25 $(OH)^2D^3$. Figure adapted from Jäpelt et al. [15].

flexibility of these seco-B ring thus facilitating the interaction of 1,25 D3 with many tissues where specific biochemical interactions that produce biological effects occur [9].

In summary, vitamin D is made up of 4 rings: A, B, C and D, with a cyclopentanoperhydrophenanthrene nucleus. In contrast to the hormonal A B C D rings, the B ring has an open structure, there is a hydrocarbon chain attached to the rings at C17 position, a hydroxyl group (OH) at C3 while 4 methyl (CH3) groups are attached at C13, C18 and C25. In all, the molecule contains 27 carbon atoms. Variants of the molecule like ergocalciferol contain a double bond between C22 and C23 and additional methyl group at C24.

7-Dehydro-cholesterol (pro-vitamin D3) is photolyzed by ultraviolet light to pre-vitamin D3 which spontaneously isomerizes to vitamin D3 (**Figure 2**). Ultraviolet radiation with wavelengths between 290 and 315 nm causes the bond between the 9th and 10th position of the steroid ring to open, forming a compound called secosterol. This further undergoes cis-to-trans isomerization, by the formation of a trans-bond between the 5th and 6th carbon atoms, leading to the formation of vitamin D3, or cholecalciferol. Vitamin D3 (cholecalciferol) is converted into calcitriol (1,25 dihydroxycholecalciferol) by a process of hydroxylation in the liver and kidneys respectively, this is the active form of vitamin D. It is this very important involvement of ultraviolet radiation in the formation of active vitamin D that leads to its appellation as the "sunshine vitamin" [10].

3.4 Physiological effects of vitamin D

Physiologically, vitamin D can be broadly said to be essential for:

i. Regulation of calcium in the body

ii. Immune-modulation

As stated above, vitamin D is essentially associated with calcium regulation and immune modulation. Because of its effect on calcium absorption regulating mineral metabolism and bone growth, it is often referred to as a hormone. Physiologically, vitamin D facilitates intestinal absorption of calcium and also stimulates absorption of phosphate and magnesium ions. In the absence of vitamin D, efficiency of dietary calcium absorption is low. Furthermore, absorption of calcium is enhanced by vitamin D by stimulating the expression of a number of proteins involved in transporting calcium from the lumen of the intestine across the epithelial cells into the blood.

The indispensable role of vitamin D in calcium homeostasis and by extension bone metabolism has been demonstrated in many in-vitro animals' experiments. As a transcriptional regulator of bone matrix proteins, vitamin D induces the expression of osteocalcin and suppresses synthesis of type I collagen [11]. Also, in cell cultures, vitamin D stimulates differentiation of osteoclasts [12]. Although these changes may not be very crucial in humans, it's however been shown that the crucial effect of vitamin D on bone is to provide the proper balance of calcium and phosphorus to support mineralization [13]. An interesting finding was that vitamin D receptors are present in most if not all cells in the body. Additionally, experiments using cultured cells have demonstrated that vitamin D has potent effects on the growth and differentiation of many types of cells. These findings suggest that vitamin D has physiologic effects much broader than a role in mineral homeostasis and bone function. As one example, many immune cells not only express vitamin D receptors, but are capable of synthesizing active vitamin D, and deficiency in vitamin D has been associated with increased incidence of autoimmune disease and susceptibility to diseases [14]. This may be the basis of the uniqueness of the chemical structure of vitamin D molecule which, because of its seco-B triene on the open B ring, allows for its flexibility that facilitates interaction with many tissues to produce various biological effects [9]. It may therefore be inferred that it is this flexibility that probably allows though empirically for its association (in its crude form) and application in the management of many diseases in Africans natives. A brief description of some of these applications is listed below:

3.5 Diseases and medicinal applications of vitamin D

Diseases of vitamin D are usually associated with its deficiency which is often due to inappropriate dietary intake or in some climates and cultural settings, due to inappropriate exposure to ultra-violet light necessary to convert the ergosterol to the pre-vitamin format at the dermal level. Conventionally, circulating level of 25 hydroxy vitamin D is used in assessing appropriateness or other wise of vitamin D in the body. Based on this, vitamin D deficiency is defined by most experts as a level of less than 20 ng per milliliter (50 nmol per liter) [16–19, 24]. Hence, a level of hydroxy vitamin D $\geq$ 30 ng per milliliter is considered normal or adequate to affect the various functions of this vitamin [16].

Since vitamin D is normally synthesized in the body, diseases due to its deficiency have not been fully ascertained. However, certain health conditions in the elderly and in some climatic and cultural situations not allowing for adequate exposure to UV light have been described. Such disease conditions include:

3.5.1 Osteoporosis

This is a condition where bone density is decreased causing weakness in the bone and its inability to carry the frame of the body. This has been reported to be prevalent amongst women and approximately 33% of women aged between 60 and

70 and 66% of those over 80 have osteoporosis [20, 25]. Reduced bone mineral density increases the risk of fractures, which significantly contributes to morbidity and mortality of older persons [21, 26]. Physiologically, vitamin D deficiency is associated with reduced intestinal calcium absorption leading to an imbalance in calcium level and attendant reduction in bone mineral content resulting in reduced bone mineral density. Although there are few exceptions, generally, treatment of osteoporosis with vitamin D supplements have been reported severally underscoring and establishing the importance of vitamin D in bone mineral contents and the diseases associated with its imbalance [22, 27]. As stated above, essentially, osteoporosis is more prevalent among women especially at the post-menopausal stage. It's been shown that the occurrence may not be unconnected with a disruption of their hormonal profile which is occasioned by the menopause. However, natives in sub-Sahara Africa (and in other areas of the world like China) had used plants and herbs for the management of osteoporosis in this group of people. For example, the fruit *Avocado* (*Persea americana*) has been used for ages in mitigating many bone diseases including osteoporosis [23, 28]. Hence, several unpublished reports on the consumption of this fruit by native Chinese and Africans to alleviate the pains of menopausal changes abound.

Physiologically, oxidative and inflammatory stress have been adduced as the pathological basis of changes in bone that eventually result in osteoarthritis and osteoporosis, avocados fruit has been found to play important role in decreasing this oxidative and inflammatory stress due to the presence of large number of xanthophyll carotenoids such as lutein and zeaxanthin which are rich in anti-oxidants. Hence, consumption of this fruit by the natives in parts of the world where they are abundant has helped in mitigating the osteoporotic effect of hypocalcaemia occasioned by a deficiency in vitamin D. Other unpublished works have also reported the presence of other vitamins (vitamins B, C, K and E) and a high concentration of potassium and magnesium in the fruit.

3.5.2 Muscle weakness

Muscle weakness is also a prominent feature of vitamin D deficiency. Impaired muscle function with non-specific muscle weakness especially in the elderly has been documented in patients to cause falls. Discovery of vitamin D receptor in skeletal muscle tissue suggestive of possible vitamin D activity even in this region may be an indication of this vitamin's involvement in muscular activity and by inference it's possible ameliorative role in non-specific muscle weakness. Although, studies on this aspect of vitamin D in terms of dosage have been equivocal, the fact that supplementation with vitamin D in this condition has produced relief in some documented cases [24, 29] lend credence to the medicinal use of vitamin D in ameliorating non-numerical specific muscle weakness.

3.5.3 Hypertension

Oral supplementation with vitamin D is becoming a common practice in the treatment of hypertension in Blacks; this was because reduced level of 25 hydroxy vitamin D was found to be common in Blacks with diastolic hypertension. Although, the mechanism of this amelioration is yet to be fully understood, the practice is gradually gaining ground amongst Blacks [25, 30]. This may be the basis of consumption of several herbal preparations which mostly contain many algae, fruits and plants like *Ocimum gratissimum* in the empirical treatment of hypertension in African natives. Unfortunately, there are no published data or scientific investigations to support some of these activities.

3.5.4 Fixing of fractures

In sub-Sahara, it is not uncommon to see fractures being fixed by native doctors using the local technology. In most of such cases, the fractured bones are pieced together in their native format and incubated at fairly warm temperatures (40–50°) after wrapping with plants leaves such as wild *Ocimum gratissimum* [26, 31] such fractures often healed up after few days (7–21 days). Further studies on this traditional method of fixing fractures using broken/fractured chicken legs have confirmed the possible efficacy of this method in the local treatment of fractures [27, 32]. Although, most of these methodologies are empirical, the possibility of enhanced osteoblastic activity due to increased vitamin D supplementation from the leaves cannot be totally ruled out. We have also applied *O. gratissimum* experimentally in rats to ameliorate the debilitating effect of lead (Pb) toxicity probably based on the antioxidant and anti-inflammatory properties of this plant [28, 33].

3.5.5 Autoimmune disorders and diseases

Recently, some autoimmune disorders like rheumatoid arthritis and multiple sclerosis have been linked with vitamin D deficiency; an increasing number of this condition is responding to vitamin D supplementation [29, 34]. Although, the mechanistic effect is not yet known, possibility of proliferation of anti-inflammatory cytokine-Tumor Growth Factor (TGF)-induced by the upregulation of calcium level due to vitamin D supplementation in these subjects remain a probable hypothesis in the physiological role of vitamin therapy in this condition.

4. Conclusion

The multipurpose application of vitamin in the management of many diseases is not in doubt; however, the biochemical and physiological basis of its application in most of the disease states where it has been used either prophylactically or curatively are still under investigation. In the sub-Sahara, as stated in the prolog to this chapter, though empirical, medicinal use of leaves especially in fixing fractures has been and is still a popular practice especially in rural communities where access to basic medical facility is limited.

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