Therapeutic effects of vitamin D and cancer: An overview

Jisha Elsa Varghese1 | Balamuralikrishnan Balasubramanian2 | Shanmugam Velayuthaprabhu3 | Velusamy Thirunavukkarasu3 | Rengasugam Lakshminarayanan Rengarajan4 | Easwaran Murugesh5 | Pappusamy Manikandan6 | Meyyazhagan Arun6 | Arumugam Vijaya Anand1

1 Department of Human Genetics and Molecular Biology, Bharathiar University, Tamil Nadu, India
2 Department of Food Science and Biotechnology, College of Life Science, Sejong University, Seoul, Republic of Korea
3 Department of Biotechnology, Bharathiar University, Tamil Nadu, India
4 Department of Animal Science, Bharathidasan University, Tamil Nadu, India
5 Nutritional Improvement of Crops, International Centre for Genetic Engineering and Biotechnology, New Delhi, India
6 Department of Life Sciences, CHRIST (Deemed to be University), Karnataka, India

Correspondence
Balamuralikrishnan Balasubramanian, Department of Food Science and Biotechnology, College of Life Science, Sejong University, Seoul, 05006, Republic of Korea.
Email: geneticsmurali@gmail.com, bala.m.k@sejong.ac.kr
Arumugam Vijaya Anand, Department of Human Genetics and Molecular Biology, Bharathiar University, Coimbatore-641 046, Tamil Nadu, India.
Email: avamiet@yahoo.com

Abstract
Since vitamin D’s discovery, strenuous efforts to investigate its physiological exploit and deficiency on human health were done. Our body synthesizes fat-soluble vitamin D when get exposed to sunlight. In recent years, experimental data indicate that sunlight exposure and an adequate level of circulating vitamin D can reduce the incidence of cancer. Several in vitro and in vivo studies also suggest vitamin D as a potentially valuable supplement for cancer treatment and prevention. Nevertheless, there need to be adequate clinical studies performed to substantiate the suppressive ability of vitamin D concerning cancer incidence. Thus, understanding the cellular mechanisms of vitamin D can be advantageous for preventing several chronic diseases. Consequently, this review concentrates on different studies that have been conducted to characterize the outcome of vitamin D in reducing cancer incidence and its medication by cellular progression mechanism.

KEYWORDS
calcitriol, cancer, cholecalciferol, single nucleotide polymorphism, vitamin D

1 INTRODUCTION

In his exemplary rickets experiments, Edward Mellanby learned about vitamin D in 1919 (Mehta & Mehta, 2002; Mellanby, 1976). Vitamin D is a family of compounds accompanied by side-chain structures having 9, 10 seco steroids. A group of fat-soluble prohormones together with their metabolites make up the vitamin D system (Tohari et al., 2019). In plants, it is seen as the photochemically synthesized vitamin D2 (ergocalciferol). While, in response to a suitable wavelength of ultraviolet B (UV B) radiation of 270–300 nm, vitamin D3 (cholecalciferol) is synthesized in the skin of animals and humans (Vuolo et al., 2012). After its reaction with sunlight, the synthesized vitamin D in the liver undergoes hydroxylation to form 25-hydroxyvitamin D (calcidiol) and in the kidney to form the physiologically active metabolite calcitriol (1,25-D3). This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

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dihydroxy vitamin D (1,25(OH)₂D), which is the hormonal form of vitamin D (Figure 1; Ali & Vaidya, 2007; Wang et al., 2017). Some foods that supplement vitamin D in the diet are fatty fish, fish liver oils, mushrooms, eggs, and dairy products (Black et al., 2017; Ness et al., 2015).

Vitamin D plays a foremost function in the calcium homeostasis in the body and thus is requisite for bone mineralization (Fleet, 2017). It substantially affects the proliferation and differentiation of cells (Khammissa et al., 2018), immunoregulation, anti-inflammatory, oxidative stress reduction, xenobiotic detoxification, anti-cancer, cardiovascular benefits, and neuroprotective functions. Patients with autism, Parkinson’s disease, schizophrenia, Alzheimer’s disease, and multiple sclerosis have low levels of vitamin D (Umar et al., 2018). Vitamin D is a dynamic antioxidant, can promote balanced mitochondrial activities, and can also prevent oxidative stress (Wimalawansa, 2019). Table 1 shows the general functions, signs, and causes of vitamin D deficiency.

Cancer is one of the most fatal diseases seen in the face of the 21st century with more than 11,00,000 new cases being reported annually in India (Bivona et al., 2019). India has a mortality rate of 79 per 1,00,000 deaths from cancer and accounts for over 6% of total deaths (World Health Organization, 2011). The top three incidence types of cancer include lung, female breast, and colorectal cancer, which account for the first, fifth, and second mortality rates amongst the top five. These three types of cancer together account for one-third of the occurrence of cancer and the worldwide mortality burden (Rajpal et al., 2018). Epidemiological observations support the main role of calcitriol in suppressing the proliferation of cancer cells (Roy, & Saikia, 2016). In some studies, it was observed that the amount of sunlight falling is inversely proportional to the incidence of both breast and colon cancer (Nair-Shalliker et al., 2013). Also, another study shows that 87% of patients with triple-negative breast cancer had insufficient serum 25(OH)D₃ levels and that the serum concentration of 130 nM or approximately 50 ng/ml 25(OH)D₃ shielded almost 50% from breast cancer (Krishnan & Feldman, 2011). Likewise, many parallel studies show an affirmative association between vitamin D levels and the occurrence of colon and prostate cancers (Freedman et al., 2008). Calcitriol helped in the reduction of tumor size, enhancement of cellular differentiation in mice grafted with human thyroid follicular carcinoma-derived cells (Kim, 2017). Thus, vitamin D is used for prevention and cancer medication.

### Mechanism of Action of Vitamin D

There are nearly about 3000 genes that are upregulated by vitamin D. In all types of human cells, receptors that respond to vitamin D are present. Table 2 represents the most common vitamin D metabolism-related genes, which when mutated affect the health conditions considerably (Figure 1). The higher exposure to vitamin D is assumed to forestall many cancers. In cancer regulation, serum calcitriol acts as an effective agent in the regulation of cell growth and differentiation as well as in neoplasm invasion and maturation, through genomic effects modulated by the vitamin D receptor (VDR) and also by non-genomic effects such as autocrine/paracrine substance metabolism. Furthermore, calcitriol is involved in anti-cancer activity, both in vivo and in vitro (Uhmann et al., 2011).

### Table 1 Vitamin D—general functions, signs, and causes of deficiency

| Vitamin D | Signs of deficiency | Causes of deficiency |
|-----------|---------------------|----------------------|
| General functions | 1. Necessary for the neuromuscular function | 1. Leads to metabolic abnormalities with the absorption or metabolism of vitamin D |
| | 2. Helps with the absorption of calcium | 2. Secondary indoor lifestyle |
| | 3. Development of bones and teeth | 3. Regular use of sunblock |
| | 4. Activates the immune system | 4. Low down stomach acid |
| | 5. Essential for the functions of thyroid | 5. Liver and gallbladder dysfunction may contribute to a deficiency |
| | 6. Helps to prevent anxiety and depression | |
### TABLE 2  Vitamin D metabolism-related genes

| Genes | Function |
|-------|----------|
| **DHCR7**<br>(7-dehydrocholesterol reductase) | Chromosomal location: 11q13.4<br>This gene synthesizes 7-dehydrocholesterol reductase. Using nicotinamide adenine dinucleotide phosphate (NADPH), by de novo synthesis this enzyme catalyses the production of cholesterol from 7-dehydrocholesterol (Ahn et al., 2010) |
| **GC (DBP)**<br>(group-specific component (vitamin D binding protein)) | Chromosomal location: 4q12-q13<br>Belonging to the albumin gene family, it is a multi-functional protein, which can bind to different kinds of vitamin D. Vitamin D metabolites are transported between skin, liver, kidney, and other target tissues via GC. During cancer treatment with vitamin D, macrophages would get triggered against these cells (Yamamoto et al., 2008) |
| **LRP2**<br>(LDL receptor-related protein 2) | Chromosomal location: 2q31.1<br>Known as megalin, endocytosis of 25(OH)D-DBP complex is primarily done by LRP2 (Fedirko et al., 2019) |
| **CUBN**<br>(cubilin) | Chromosomal location: 10p13<br>CUBN acts as a chief co-receptor in the megalin associated endocytic pathway. Abnormal 25(OH)D metabolism is linked with improper functioning of CUBN (Nykjaer et al., 2001) |
| **CYP2R1**<br>(cytochrome P450, family 2, subfamily R, polynucleotide 1) | Chromosomal location: 11p15.2<br>CYP2R1 is a mono-oxygenase and is involved in drug metabolism and synthesis of cholesterol, steroids and lipids. An inherited mutation in the codon 99 of the CYP2R1 gene, results in the substitution for a proline for a leucine which eliminates the enzymatic activity. This mutation is also connected with low serum levels of 25(OH)D and its symptoms (Cheng et al., 2004) |
| **CYP24A1**<br>(cytochrome P450, family 24, subfamily A, polynucleotide 1) | Chromosomal location: 20q13.2<br>The degradation of calcitriol is a result of hydroxylation reactions given by the enzyme produced by this gene. Also, this enzyme has a vital part in calcium homeostasis and the vitamin D endocrine system by the maintenance of vitamin D3 levels (Genetics Home Reference, 2020) |
| **CYP27A1**<br>(cytochrome P450, Family 27, Subfamily A, polynucleotide 1) | Chromosomal location: 2q35<br>It is a gene encoding enzyme for synthesizing, transporting and degrading vitamin D. This enzyme aids in the degradation of cholesterol to bile acids and can also hydroxylate vitamin D3 making it a precursor to calcitriol (Tieu et al., 2012) |
| **CYP27B1**<br>(cytochrome P450, family 27, subfamily B, polynucleotide 1) | Chromosomal location: 12q14.1<br>Being present in the kidney, this gene provides instructions for making an enzyme, 1α-hydroxylase, that catalyses the hydroxylation of calcidiol to calcitriol (Takeyama et al., 1997) |

### 2.1 Genomic and non-genomic pathways

Vitamin D’s most exclusive aspect is its connection with definite nuclear receptors. After the ligand is associated, a set of events of signal transduction is inaugurated, leading to its function (Figure 2; Guo et al., 2018). Vitamin D has two conspicuous ways of action, namely, first, binding to a specific protein receptor (VDR) and second, using functions linked with non-genomic membranes (Falkenstein et al., 2000), where the latter actions take place within minutes when compared to the former actions that take a longer time to respond. Both of these courses, when sustained with enough evidence, proved to be quite efficient (Jones et al., 1998).

### 2.2 Genomic actions of vitamin D

The VDR is explicitly expressed by both benign and malignant proliferative cells. Following the entry into the particular tissue, vitamin D bound to VDR forms heterodimers with the retinoid X receptor (RXR); when a ligand binds to this dimer, they attach themselves to a complex of particular sequences of nucleotides called vitamin D response elements (VAREs).
components (VDRE). VDRE is usually found at the promoter region for vitamin D-regulated gene, but in some cases, VDRE is present several kilobases distal to the transcription start sites. When this complex binds to the DNA, several transcriptional modulating proteins are recruited, and these exchanges allow VDR to upregulate or downregulate the gene expression (Figure 3; Duffy et al., 2017; Feldman et al., 2014). Genes such as CYP24A1, BGLAP (osteocalcin), and cyclin-dependent kinase inhibitor 1A (CDKN1A, encoding p21Waf1/Cip1) are transcriptionally stimulated by calcitriol (Deeb et al., 2007).

2.3 | Non-genomic action of vitamin D

The non-genomic action is fast, independent of transcription, and may affect it indirectly through cross-talking with other pathways (Nemere et al., 2004). Non-genomic steps are initiated with a non-classical membrane receptor and a calcitriol receptor (membrane related, rapid repression steroid-binding) named 1,25D3-MARSS (Norman, 2006). Rapid calcium translocation through the intestinal mucosal membranes is induced through the non-genomic actions of calcitriol. The binding of calcitriol in the plasma membrane, along with the phospholipase C, protein kinase C (PKC), G protein-coupled systems, leads to one or more messenger system’s activation of phosphoinositide 3-kinases. Among its various results like opening calcium or chloride channels with voltage-gated or second-generation messengers, some in particular, like the RAF kinase / Mitogen-activated protein kinase (RAF/MAPK), may adjust the crosscutting of the genetic expression regulation nucleus: Extracellular signal regulated kinase (ERK) can increase VDR transcriptional activity and VDR can also be stabilized by non-genomic activation of PKC via phosphorylation (Morelli et al., 2001).

3 | Anti-cancerous effects of vitamin D

3.1 | Anti-proliferative effect

Calcitriol causes an anti-proliferative result by effectuating the arrest of the cell cycle in the G0/G1 phase in the following ways: by elevating the execution of CDK inhibitors, through the p53-dependent method; by hypophosphorylation of the retinoblastoma protein; by reducing the CDK2 activities (Flores et al., 2010); interdiction of mitogenic signaling (Boyle et al., 2001); intensifying the growth inhibitors’ expression (Welsh, 2012); balancing the intercellular kinase pathways; the subjugation of proto-oncogene MYC (Rohan, & Weigel, 2009). Calcitriol with its analogs restrains the elevated activity of telomerase in cancer cells by curtailing the telomerase reverse transcriptase mRNA (Hisatake et al., 1999).

3.2 | Induction of apoptosis

Calcitriol generates apoptosis by hindering it in the mammary epithelia (Matthews et al., 2010). In several types of cancers, apoptosis is triggered by cell-specific mechanisms (Simboli-Campbell et al., 1997). By the protease pathways, it also starts the downstream events (Blutt et al., 1997).

Usually, in cancer cells, apoptotic pathways are inhibited so that cancer cells can survive longer and mutations can get accumulated. As a result of the gene regulation of vitamin D, in breast cancer cell lines (MDA-MB-231 and MCF-7), colorectal cancer cell lines (LoVo, HT29, and HCT116) and prostate cancer cell lines (LNCaP, DU-145, and PC-3) help in the upregulation of pro-apoptotic genes like BAX, BAK1, BAG1, while it downregulates the anti-apoptotic genes like BCL-2, BCL-XL and several survival genes in several cancer cell lines (Feldman et al., 2014). Hindrance to apoptosis throughout the development of mammary epithelia in VDR (Vdr)-null mice show that during the normal mammary gland development, the process of apoptosis plays a significant role in the remodeling of surrounding stroma and re-differentiation of adipocytes (Feldman et al., 2014; Matthews et al., 2010; Watson, 2006). In several types of cancers, apoptosis is triggered by cell-specific mechanisms (Simboli-Campbell et al., 1997). By the protease pathways, the downstream events also start. From these findings, it can be suggested that vitamin D exerts some beneficial actions on different cancer types.

3.3 | Stimulation of differentiation

In feedback to 1, 25(OH)2D, a few cancer cells develop a less metastatic with mature phenotypes (Gocek, & Studzinski, 2009). The
4 | Anti-inflammatory effect

Inflammation is an instigating factor for the progression of many cancers, where calcitriol displays favorable anti-inflammatory measures (Feldman et al., 2014). Some of its main mechanisms are (1) repression of prostaglandin synthesis as well as prostaglandin signals (Krishnan & Feldman, 2010); (2) suppression of p38 stress kinase by upregulation of MAPK phosphate 5 and ensuing hindrance of pro-inflammatory cytokine (Nomm et al., 2006); (3) constraining of signalization of NF-κB & Feldman, 2010); (2) suppression of p38 stress kinase by upregulation of MAPK phosphate 5 and ensuing hindrance of pro-inflammatory cytokine (Nomm et al., 2006); (3) constraining of signalization of NF-κB (Cohen-Lahav et al., 2006).

4.1 | Inhibition of invasion and metastasis

Calcitriol inhibits invasion and metastasis by the regulation of plasminogen activator system components as well as matrix metalloproteinases (MMPs; Koli & Keski-Oja, 2000); lowering tenascin C182, α6 integrin, and β4 integrin expressions (Sung & Feldman, 2000); suppression of MMP9 activity (Koli & Keski-Oja, 2000); and an escalated expression of E-cadherin (Campbell et al., 1997).

4.2 | Inhibition of angiogenesis

Vitamin D suppresses angiogenesis through the restriction in the expression of the vascular endothelial growth factor (VEGF), by transcriptional repression of the hypoxia-inducible factor 1 alpha (HIF1A) (Semenza, 2010) and interleukin-8 (IL-8; Bao et al., 2006); direct reducing effect of calcitriol on endothelial cells and an indirect procedure by reducing prostaglandin E2 (PGE2) generated by cyclooxygenase 2 (Fukuda et al., 2003).

Vitamin D inhibits invasion and metastasis by the regulation of plasminogen activator system components as well as MMPs (Koli & Keski-Oja; 2000); lowering α6 and β4 integrin expressions (Sung & Feldman, 2000) and an escalated expression of E-cadherin and tissue inhibitor of metalloproteinase-1. Angiogenesis is a physiological process by which new blood vessels are formed from pre-existing ones. Both normal and cancer cells require oxygen and nutrients for growth, which is provided by blood vessels. In developing cancer cells, endothelial cells are dynamically vigorous due to the presence of proteins like epidermal growth factor, acidic and basic fibroblast growth factors, IL-8, prostaglandin E1 and PGE2 (proangiogenic factors), and VEGF, are the most potent stimulator), which activate endothelial cell growth (Rajabi & Mousa, 2017). Vitamin D is observed to hinder endothelial cells activation, proliferation, migration, and tube formation (Kalkunte et al., 2006). During hypoxia, initiation of angiogenesis occurs with leads to the synthesis of proangiogenic factors that will activate the signaling cascades. Stimulation of angiogenesis is mediated by the HIF1A, which will indeed increase the VEGF and proangiogenic factors expression. Vitamin D suppresses angiogenesis through the restriction in the expression of the VEGF by transcriptional repression of the HIF1A and IL-8 and explicitly impedes the proliferation of endothelial cells guiding to the inhibition of angiogenesis (Krishnan et al., 2012).

5 | Polymorphism of VDR

Genetic surveys have pointed out associations linking some cancer histotypes with the observation of certain single nucleotide polymorphism (SNPs) of the VDR gene, CYP24A1, and CYP27B1. About 200 various related SNPs VDR are additionally linked with tumorigenesis are Fok1, Bsm1, Taq1, Apa1 polymorphisms, where the former two being vastly researched about. Situated in the coding region of the VDR gene, Fok1 polymorphism makes a protein that is longer than three amino acids, wherein the shorter one shows sharp power (Vuolo et al., 2012). The Bsm1 polymorphism, located in the gene’s 3-end, is associated with a poly (A) repeat, which can influence the RNA stability (Touvier et al., 2011; Bai et al., 2012). Cancer along Bsm1 and Fok1; prostate cancer with Bsm1, Fok1, Apa1; breast cancer along Bsm1, Fok1, Taq1 have shown substantial connections (Chen et al., 2009; Raimondi et al., 2009).

6 | Epidemiological shift regarding vitamin D and cancer

Many epidemiological kinds of research have displayed a reverse association between UV B and cancer incidence. Nevertheless, vitamin D’s role in this is dubious, as the content of vitamin D in diet differs favorably (Garland et al., 2006). Thus, it is more appropriate to examine the calcitriol serum levels and cancer formation, folocking mainly on what dosage of vitamin D is needed to protect one from cancer. Amidst all epidemiological surveys, estimation of the levels of the symptomatic levels of calcidiol was given more importance. With acclimatization of other factors, a 30%–40% lowering of colorectal cancer was seen in patients with high levels of calcidiol, when compared to patients administered with its low levels (Lee et al., 2011). But clear bonds are ambiguous for other types of cancers. For instance, a contemporary analysis showed no or less relation between the levels of calcidiol to prostate cancer (Gilbert et al., 2011) or negative association with the levels and breast cancer (Chlebowski et al., 2008). Some investigations indicate that significant amounts of calcidiol before or during therapy may enhance the survivability of many cancers. For example, patients with a low calcidiol quartile had a 60% higher mortality rate and a significantly lower risk of prostate cancer in those administered with its high doses (> 30 ng/ml; Fedirko et al., 2012). Another survey inspected the association of VDR-SNP with cancer risk, where there was an association with VDR-SNP with colorectal, prostate, and breast cancer (Bai et al., 2012), but these surveys have not produced enough data concerning other types of cancers.
6.1 | Effect of vitamin D in the animal model

Animal models give convincing evidence for the job of calcitriol in the elimination of unchecked hyperplasia as well as tumor formation caused by neoplasia (Bouillon et al., 2008). A notable decrease in tumor development and stress is seen when dietary vitamin D, calcitriol, and its analogs are administered, which indicate its defensive role against cancer (Zinser et al., 2002). Vitamin D along with calcium, supplied by food, suppresses tumor formation and growth (Hummel et al., 2013), whereas its deficiency in the diet speeds up tumor growth regardless of calcium levels (Ray et al., 2012). The higher levels of calcidiol, supplied through diet, cause significant tumor inhibition, which appears to be sufficient to aid in the normal homeostasis of minerals and bone health. Data has also shown that increased levels of vitamin D than in the bones are necessary for cancer prevention and supporting the fact that calcitriol is useful for cancer treatments (Krishnan et al., 2012).

6.2 | Clinical trials

Additive effects were found with combinations of vitamin D and other conventional chemotherapeutic factors (Bouillon et al., 2006). Randomized controlled studies (RCTs) were conducted, which showed a 60% decrease in cancer invasion when a dosage of 1100 IU/d of vitamin D₃ along with 1.450 mg/day of calcium was given to post-menopausal women (Garland et al., 2009; Lappe et al., 2007). More or less, the incidence reductions for all cancer types were because of vitamin D₃, and partially, due to calcium intake. Some examinations put forward that calcitriol could have a curative benefit. However, the RCT results were not conclusive, since many people had already begun taking vitamin D supplements, fabricating difficulties in gathering randomized participants; and how different people responded to vitamin D treatment, which is controlled by the VDR-SNPs, CYP24A1 and CYP27B1 (King et al., 2010).

However, it remains to identify the optimal biological dosage of vitamin D or the concentration of calcitriol in patients. Moreover, many clinical trials are still in different phases and yet to be completed. Some of the recent findings from these studies show a positive outcome regarding the usage of treatment with vitamin D. Despite substantially higher levels of serum 25(OH)D in the vitamin D treated group, this was not allied with any noteworthy outcomes on tumor proliferation or apoptosis. These deductions are dependable with the shortage of benefit observed in potential prevention trials (trial registration: clinicaltrials.gov NCT01948128; Arnaout et al., 2019). A modified high-dose oral vitamin D supplementation securely tolerates a higher percentage of the serum 25(OH)D level standardization associated with a standard regimen in chemotherapy-treated Early breast cancer (EBC) patients. As conformity to a daily oral supplementation endures poor in this setting, an adaptation of the treatment schedule is warranted (clinical trial number: NCT01480869; Jacot et al., 2016). In the randomized clinical trial, supplementation with vitamin D lowered the frequency of progressive (metastatic or fatal) cancer in the overall cohort, with the sturdiest risk lessening seen in individuals with normal weight (trial registration: ClinicalTrials.gov Identifier: NCT01169259; Chandler et al., 2020).

7 | Conclusion

Vitamin D is the progenitor of calcitriol as well as an important calcitropic hormone. Various analytical studies have attracted considerable attention to the job of vitamin D in cancer prevention. Many but not all lines of evidence reveal the increase in mortality and cancer risks with other chronic diseases linked with vitamin D deficiency. Directly or indirectly, calcitriol helps in the regulation of a large number of genes amenable to cellular activities. Albeit many epidemiological tests show a negative connection between vitamin D and UV B status with cancer, this connection has not been confirmed. Many rodent trials have shown that calcitriol or its analogs can decrease in vivo growth; however, human trials for this have not been available. Last, large RCTs are required to show that vitamin D lowers cancer incidence and improves cytotoxic therapy. Meanwhile, a sufficient vitamin D status should be necessary for all, which can help prevent malignancy.

8 | RECOMMENDATION

Vitamin D can be fully used in cancer therapy with enough proof regarding the cellular mechanism involved in it. Each cellular component should be evaluated for the study and its effect on vitamin D should be found. This can help in the development of promising medicine for different cancers.

AUTHOR CONTRIBUTIONS

Conceptualization: Arumugam Vijaya Anand and Balasubramanian Balamuralikrishnan. Writing—original draft preparation: Jisha Elsa Varghese, Shanmugam Velayuthaprabhu, and Velusamy Thirunavukkarasu. Selected bibliographic sources: Rengasamy Lakshminarayanan Rengarajan, Easwaran Murugesh, Pappusamy Manikandan, and Meyyazhagan Arun. Coordinated the working group: Balasubramanian Balamuralikrishnan and Arumugam Vijaya Anand. Writing—review, editing, and proof reading: Velusamy Thirunavukkarasu, Meyyazhagan Arun, and Arumugam Vijaya Anand, Balasubramanian Balamuralikrishnan. This review article was carried out in collaboration with the authors. Balasubramanian Balamuralikrishnan contributed as the first author. All authors made significant contributions to this article. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

The authors have no conflict of interest.

ORCID

Balamuralikrishnan Balasubramanian @ https://orcid.org/0000-0001-6938-1495
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