



## Targeting Wnt/B-Catenin Signalling Pathway by Natural Substances Regarding The Therapy of Osteoporosis & Cancer:- A Review

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### Abstract

Osteoblasts are basically obtained from mesenchymal stem cells (MSC's) in the bone marrow (BM). Such stem cells are capable of differentiating into osteoblasts, that possess the working of liberating bone matrix, facilitating bone generation & take part in bone remodelling. The abnormality of osteoblasts are capable of leading to several bone-associated diseases, inclusive of i) osteoporosis, ii) postponed fracture healing, in addition to iii) skeletal aberrations. In recent decades, with the inimical sequelae resulting by the employment of PTH agents, bisphosphonate agents, along with calmodulin agents, scientific researchers have performed greater deeper work in reference to the mechanistic modes of osteoblast differentiation, as well as are actively searching for natural substances regarding the therapy of osteoporosis. The Wnt/ $\beta$ -catenin signalling pathway is believed to be one of the significant pathways of osteoblast differentiation, in addition to has assumed a significant target for the therapy of osteoporosis. The Wnt/ $\beta$ -catenin signalling pathway, in case its activation is escalated or inimicality of its expression takes place, would result in several diseases inclusive of tumours. Subsequent to reviewing anatomy of the human skeleton & factors modifying its development/regeneration, therapeutic application of Gut Microbiota & metabolites & avoidance & treating Osteoarthritis & bone associated diseases, pharmacological as well as non-pharmacological fracture risk management for optimizing fractures prevention in potential osteoporotic women (Post menopausal and peri menopausal women & several modes of cancer avoidance & therapy (howlnc RNAsCYTOR markedly expressed in CRC controls $\beta$ -catenin and colon cancer metastasis). here our objective of this review is to provides a summary of the action of Wnt/ $\beta$ -catenin signalling pathway on osteoblast differentiation as well as the association amongst the associated proteins in the pathway in addition to human diseases. Simultaneously, the latest propagation of work on natural substances targeting Wnt/ $\beta$ -catenin signalling pathway against osteoporosis is described.

**Keywords:** Wnt/B-Catenin Signalling Pathway, Osteoporosis, Cancer

### 1.Introduction

Osteoporosis is a disease of the skeleton resulting basically by a disequilibrium in the amount /working of osteoblasts as well as osteoclasts [1].

### Osteoporosis Possesses The Characteristics Of

- i) Diminished bone mass
- ii) Decreased bone mineral density (BMD)

iii) In addition to bone getting thinned out, affects working that enables the bones predisposed to damage along with fracture as well as thereby robustly impacting the quality of life (QOL) [2]. Osteoblasts possess a meaningful part in the generation of osteoporosis. Once osteoporosis takes place, the generation as well as actions of osteoblasts is robustly impacted resulting in diminishing in the generation/ quality of new bone tissue. This results in bones to becoming fragile in addition to sustenance of injuries with ease, escalating the risk of fracture.

#### **The basic working of osteoblasts are inclusive of facilitating**

i) bone generation, with ii) sustenance of bone density, along with iii) strength, iv) healing bone injuries, as well as take part in the controlling of bone metabolism [3]. They assist in guaranteeing bones stability in addition to keeping bones healthy by persistently generating new bone tissue. In the therapy of osteoporosis facilitating the development along with actions of osteoblasts possesses the capability of aiding in escalating bone density in addition to diminishing fracture risk, thereby leading to symptomatic improvement of osteoporosis [4]. Thereby getting insight into the differentiation event of osteoblasts is significant in reference to avoidance of along with therapy of osteoporosis.

Osteoblast differentiation delineates considerably complicated event, implicating in plethora of signalling pathways as well as governors for instance i) Bone morphogenetic proteins (BMP)- in addition to ii) The Wnt/ $\beta$ -catenin (Wnt/BC) signalling pathways [5,6]. Of these the Wnt/BC signalling pathway is believed to be one of the maximum significant along with vital differentiation pathways, along with aberrant activation/ hampering of the (Wnt/BC signalling pathway possesses the capacity of resulting in generation of bone- associated diseases for instance i) osteoporosis in addition to postponed fracture repairing [7]. Getting insight into the differentiation of osteoblasts is vital in reference to avoidance of along with therapy of associated diseases in addition to, generate efficacious avoidance along with therapy of osteoporosis. The study of Wnt/BC signalling pathway apart from aiding in getting insight into the differentiation mechanistic modes of osteoblasts, however further yield significant cues in reference to therapy of associated osteoporosis as well as generate greater efficacious avoidance as well as approaches for therapy. Agents utilized regarding osteoporosis therapy are inclusive of i) the ones which hamper bone resorption, ii) the ones which facilitated bone generation, in addition to iii) anabolic agents [8]. Nevertheless, the correlated inimical sequelae restrict their utility for osteoporosis therapy with urgency of inventing innovative therapies in reference to osteoporosis. In the meantime studies have observed that natural substances possess controlling actions on the Wnt/BC signalling pathway, illustrating the capacity of controlling bone morphogenesis by influencing the constitution or

actions of the Wnt/ $\beta$ -catenin signalling pathway. The Wnt/BC signalling pathway is anticipated to assume a therapeutic target. Nonetheless, the mechanistic modes by which natural substances control Wnt/ $\beta$ -catenin signalling continue to be uncharted.

There is existence of requirement of future studies unravelling molecular mechanistic modes in considerably greater detail as well as to isolate particular substances which possess therapeutic plausibility. Despite natural substances have illustrated plausibility regarding manipulating Wnt/ $\beta$ -catenin signalling in laboratory studies, there is existence of obstacles, even presently in reference to translating them into clinical therapies, in addition to natural substances from variable facilities might possess quality variations that influence the dependability of their therapeutic actions. Owing to this, evaluation of the manner natural substances controls the Wnt/BC signalling pathway apart from getting insight to the mechanistic modes of bone metabolism in addition is significant in reference to observations in the innovative therapies of osteoporosis.

Subsequent to reviewing anatomy of the human skeleton & factors modifying its development/ regeneration,, therapeutic application of Gut Microbiota & metabolites & avoidance & treating Osteoarthritis & bone associated diseases, pharmacological as well as non-pharmacological fracture risk management for optimizing fractures prevention in potential osteoporotic women (Post menopausal and peri menopausal women, where we had detailed role of Receptor Activator of nuclear factor  $\kappa$ B ligand (RANKL) & osteo protegrin (OPG) etc. we detailed how platelets & macrophages, liberate a cascade of cytokines of various kinds, that results in activation of a cascade of processes to get the repair started. These are inclusive of proinflammatory interleukin S-1 (IL-1), IL-6, IL-8, and IL-12], TNF $\alpha$ , C(APC), monocyte MCP1, macrophage colony stimulating factor (M-CSF), RANKL), and (OPG) [1,30, 31]. Metalloproteinases (MMP's) along with angiogenic growth factors like endothelial growth factor (VEGF) play a significant part in the total bone healing event [1,30,31]. Never the less, the modulators liberated carrying maximum significance that possess a direct action on the progenitor cells to go via the event of mitogenesis as well as osteoblastic differentiation are platelet derived growth factor (PDGF), Fibroblast growth factor (FGF), insulin -like growth factor (IGF) transforming growth factor beta (TGF- $\beta$ ) proteins, that are inclusive of Bone morphogenetic protein (BMP)- [2,4,6,7]. Further In case of bone tissue engineering, various studies in 2dimensional (D) flow systems documented the mechanical stimulation of Osteogenesis in the absence of Osteogenic supplements, that is inclusive of dexamethasone,  $\beta$ -glycerophosphate in addition to ascorbic acid or bone morphogenetic protein 2(BMP2). Like as early as 1h following perfusion Osteoblast precursors, MCT3-E1, responded to shear stress at 2 Pa by up regulation of a critical transcription factor, Runt -related transcription factor

(RUNX2), for Osteogenesis. Moreover, the up regulation of other Osteogenic markers like type 1 collagen (Col1), osteocalcin (OCN), alkaline phosphatase (ALP), was seen following 3d of persistent perfusion [rev in 20]. Akin to that mesenchymal stem/stromal cell (MSCs) were documented to go via Osteogenesis is simply secondary to mechanical stimuli. In case of studies where human bone marrow obtained MSCs documented that shear stress at 0.4 -2 Pa 2.2 escalated by the expression of BMP2, bone sialoprotein (BSP) osteopenia (OPN), as well as ALP was seen along with escalated calcium getting deposited in 7days & role of Bone marrow mesenchymal stem cells (BMSCs), several modes of cancer avoidance & therapy (howl Nc RNAs CYTOR markedly expressed in CRC controls  $\beta$ -catenin and colon cancer metastasis) & more recently crosstalk of IGF's & IGFBP's with Wnt/BC signalling pathway this here our objective of this review is to provides a summary of the action of The Wnt/BC signalling pathway on osteoblast differentiation as well as the association amongst the associated proteins in the pathway with all the components of this signalling pathway individually to get insight on this signalling pathway in addition to human diseases [9-20].

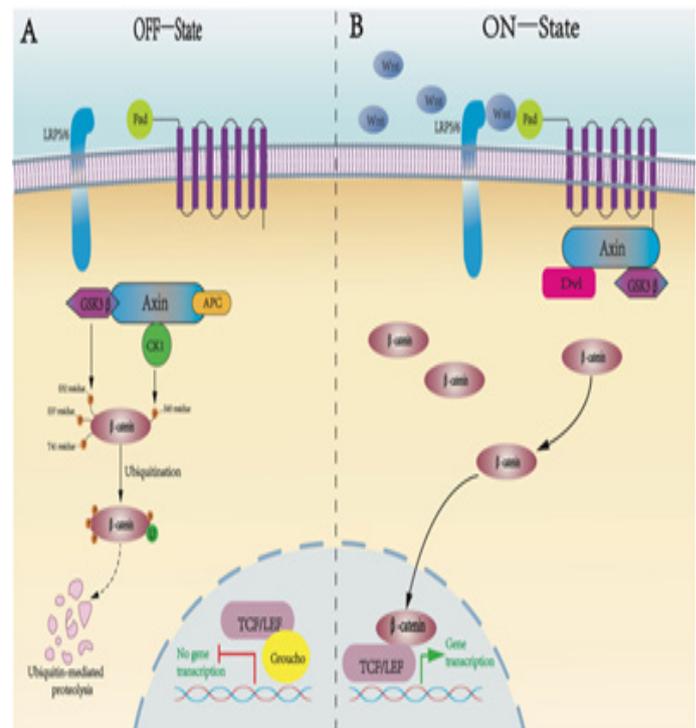
## 2. Wnt/ $\beta$ -catenin signalling pathway

in case of i) eliminated Wnt signalling / the Wnt receptor barricaded, i) binding of the Axin- APC - Gsk3 $\beta$  - casein kinase 1 $\alpha$  (CK1 complex) will take place to the free  $\beta$ -catenin in the cytoplasm along with ii) phosphorylate  $\beta$ -catenin, iii) which would be broken down by the proteasome in the cytoplasm in addition to iv) therefore does not possess the capacity of entering the nucleus [21,22]. Within the nucleus, i) the lymphoid enhancer binding (LEF)/T cell factor (TCF) transcription factor family binding takes place to the transcriptional repressor Groucho to ii) generate a complex protein structure iii) which does not possess the capacity of working on downstream target genes, which leaves the cell surface in a germanely quiet state [23].

i) In the existence of Wnt signalling, ii) Wnt generate a complex with the Frizzled (Fzd) receptor, iii) along with the co-receptor LRP5/6 on the cell membrane, surface a ligand-receptor complex called the 'signalosome' is generated. iv) activating intracellular Dishevelled (Dvl) Dvl proteins, along with v) their [24]. Fzd receptors are seven-pass-transmembrane receptors that possess an extracellular cysteine-rich domain (CRD) along with an intracellular PDZ-binding domain, of which there are ten acknowledged paralogues in humans [19,23]. Subsequent to this binding to Terminus it phosphorylates the PDZ as well as DEP sites of Fzd of the Dvl protein, along with the DIX of Dvl crosstalk's with the DIX site of Axin to result in cell membrane enrolment of Axin, while the kinases GSK-3 as well as CK1, that bind to Axin, are further translocated to the membrane in addition to phosphorylate the PPPSPxS region at the C-terminal end of LRP5/6, blocking the phosphorylation of  $\beta$ -catenin by

GSK-3, along with cause avoidance of the generation of the Axin-APC-GSK-3-CK1 complex [25].

Resultantly  $\beta$ -catenin does not possess the capacity of getting broken down normally as well as aberrant accrual takes place in the cytoplasm. Considerably greater quantities of free  $\beta$ -catenin enter the nucleus to disturb the complex protein generated by the LEF/TCF family as well as the Groucho that delineates transcriptional suppressor in addition to binds to transcription factors of the LEF/TCF family, whereas enrolling transcriptional cofactors to further activate the transcription factors, therefore activating the expression of target genes that lie downstream [26]. (see Figure. 1 [27]).



Legend for Figure 1

Courtesy [25] The canonical Wnt/ $\beta$ -catenin signalling pathway: mechanistic modes in shut off as well as on states. A In the case of lack of Wnt ligands, the Wnt/ $\beta$ -catenin signalling pathway is in the shut off -stage (OFF-State). during such time, a complex meant to disturb disturbance complex comprising of GSK3 $\beta$ , Axin, APC, in addition to CK1 leads to phosphorylation of  $\beta$ -catenin. The phosphorylated  $\beta$ -catenin gets broken down by ubiquitination. In the nucleus, in the lack of  $\beta$ -catenin the LEF/TCF family of transcription factors binding takes place with Groucho that delineates the transcriptional repressor along with suppresses the expression of target genes. B Wnt / $\beta$ -catenin signalling is active in the existence of Wnt ligand (ON-State), that binds to LRP5/6, Fed co-receptors, following which it leads to enrolment of Axin, GSK3 $\beta$ , in addition to Dvl, causing avoidance of the phosphorylation of  $\beta$ -catenin, and thereby causing avoidance of the generation facilitating of the breakdown complex. In the nucleus,  $\beta$ -catenin binds to transcription factors

of the LEF/TCF family for facilitating the expression of target gene. Abbreviations- APC -adenomatous polyposis coli. Gsk3 $\beta$  -glycogen synthase kinase 3  $\beta$ CK1 complex - casein kinase 1 $\alpha$ ; Dvl-Dishevelled LEF/TCF- T-cell factor/lymphoid enhancer factor.

## 2.1 Wntless -Related Integration Site (Wnt)

Wnt proteins portray a large family of liberated glycoproteins which possess significant parts in cell as well as growth of tissues as well as production [28]. Wnt proteins get lapidated in the endoplasmic reticulum by the O-acyl transferase Porcupine (PORCN) whereas getting intracellularly transported along with liberated through the membrane protein Wantless (WLS) [29]. Taken together the mechanistic modes of Wnt proteins is categorized into two canonical pathways: (a) the  $\beta$ -catenin based - pathway along with (b) the  $\beta$ -catenin- autonomous pathway, which is subdivided into two kinds types, inclusive of i) the planar cell polarity pathway (PCP) in addition to, the ii) Wnt/Ca<sup>2+</sup> + pathway [30,31]. Plethora of kinds of Wnt proteins are acknowledged, inclusive of Wnt1-19, among which the i) Wnt1 gene was the initial Wnt gene, got inaugurated in 1982 whereas on evaluating *Drosophila melanogaster*, in addition to Wnt 5 an apparently was the main major ligand of the non- canonical pathway [30,31].

Never the less, in contrast to the  $\beta$ -catenin autonomous pathway, the  $\beta$ -catenin- based pathway has been evaluated to a larger magnitude. Such variable kinds of Wnt proteins possess separate parts in i) biological growth, ii) generation, as well as iii) energy metabolism. Thereby, also research on Wnt proteins possess the capacity of imparting deeper insight into the phenomenon in addition to generation of diseases, that possess the capacity of driving the therapy of associated diseases. Variable kinds of Wnt proteins possess variable parts in generating disease along with therapy. For instance, i) Wnt1 is intricately correlated with tumour diseases.

1)[32] Documented that that Wnt-1 was correlated with the grade along with stage of endometrial cancers, with membranous Wnt-1 negatively correlated with high-grade endometrial cancers, whereas cytoplasmic Wnt1 was positively correlated [32]. Earlier we had reviewed the different endometrial cancers (EC), The endometrioid adenocarcinoma was the most common histologic type of (EC), that accounts for roughly 70-80% EC. This endometrioid cancer cohort was classified into polymerase-E exonuclease domain (POLE EDM), mismatch repair deficiency (MMRD), p53 abnormal (p53-abn) and p53 wild type (p53wt) groups (EEC0&further subclassified as per stage &grade-rest were only 5-10&serous 1-5% clear cell cancers, histologic types

[33].

2)Additionally, regarding cervical cancer, [34]. observed that overexpression of NEK2 that portray a serine/threonine kinase that is implicated in mitosis) i) facilitates the generation of cervical cancer as well as ii) influences the sensitivity of cervical cancer to radiation therapy by iii) activating the Wnt/ $\beta$ -catenin signalling pathway via Wnt1[34]. Earlier we had shown via Wnt signalling cascades the canonical pathway is the one most examined for its role in cancer formation. publications suggest a contribution of cancer stem cells (CSC's) in the maintenance of these cells via the WB signalling pathway. Apoptosis gets induced in CC along with inhibition of tumour growth occurs on suppression of WB pathway. Conversely over activation of WB pathway is related to cervical tumorigenesis with HPV infection [High ALDH1 activity levels were seen in a subpopulation of subjects with CC having a high ability to get self-renewed, >differentiation potential, high tumorigenicity, as seen in CSCs Further SOX2-positive cervical cells enhanced the levels of OCT4, BMII and ALDH1 stemness markers, along with in form of Vimentin, SNAII and  $\beta$ -catenin (mesenchymal SC markers. Typical phenotypes of putative CCSC were CD49f+, CK17, p63+, AII+ and ALDH; the sphere culture showed a stemness state, specified by the presence of OCT4, NANOG and  $\beta$ -catenin. Activation of Wnt/ $\beta$ -catenin and Akt signalling pathways in TWIST overexpressing cells which had CSC Properties like atmosphere formation and ALDH1 and CD44 expression levels was observed [35]. 3) Conversely, Song et al. [36], observed that the microRNA miR-130a-3p (miR- 130a-3p) directly targets Wnt1, as well as miR-130a-3p possess the capacity of hampering colorectal cancer (CRC) growth by diminishing Wnt1 expression, pointing to a plausible microRNA- dependent therapeutic approach [36].

i)The Wnt2 is believed to be a proto-oncogene protein in addition to is a tumour marker for 1) gastric, along with2) CRC, as well as greater expression of Wnt2 anticipates an inimical prognosis for colorectal as well as gastric cancer [37-39]. We had illustrated that lnc RNAs CYTOR is markedly expressed in CRC generates a positive feed forward loop with  $\beta$ -catenin along with takes part in the control of colon cancer metastasis [40]. Additionally, Wnt-2 has further been correlated with immune competence. Apart from that [41]. Illustrated that Wnt-2 liberated by cancer-associated fibroblasts (CAFs) hampers dendritic cell- manipulated antitumour T-cell reactions via the Suppressor of cytokine phosphorylated signalling 3 (SOCS3) /p-JAK2(phosphorylated [p] Janus kinase) / p- p-Signal Transducers and Activators of Transcription (STAT3), signalling stepwise pattern [41]. iii)Wnt3 possesses a part a) in embryonic

formation as well as b) neural tube generation [42], observed that Wnt3 is intricately correlated with generation of a human genetic condition namely tetra-amelia, where total lack of all limbs takes place in the form of a main characteristic [42]. Furthermore, Wnt-3 possesses significant parts in c) radiation injury in addition to radiation tolerance [43], observed that Wnt3 apart from facilitating rectification of intestinal stem cells [13] low-dose radiation, however, further possesses a pivotal parting the f) inflammatory response, along with g) plausible demise of animals resulting from greater radiation dosage. Such observations documented that that the Wnt3/ $\beta$ -catenin pathway might possess double parts that are getting controlled by variable dosage of radiation, that further possess the capacity of working meaningfully in the form of a factor in aggravating the injury once the radiation dose surpasses a particular threshold [43]. iiid). observed that chronic activation of the G protein-coupled oestrogen receptor (GPER) facilitates the proliferation of intestinal stem cells (ISCc) at the time of menopause, an event that get modulated by the liberation of Wnt-3 by Paneth cells in reference to activation of the Wnt BC signalling pathway, that escalates stem cell proliferation [37,38]. b). Additionally, hepatocyte nuclear factor 4 alpha (HNF4 $\alpha$ ) was observed to be a regulator upstream of Wnt3 as well as Paneth cells, an observation which possesses meaningful repercussions regarding getting insight into the intestinal liberation of health [44]. reviewed by us in details in role of MO. In collectively conclusion, Wnt proteins possess variable as well as multifaceted parts in variable diseases, emphasizing the complicated nature of such signalling molecules. Future studies need to be pursued to be capable of elucidating mechanistic modes of variable Wnt proteins in disease generation, as well as their plausible implementation in clinical treatment, in the anticipation that innovative therapeutic targets possess the capacity of getting isolated or associated diseases as well as positively influence patient health. in addition

The WB signalling pathway possesses a pivotal part in bone homeostasis i) by resulting in alignment of the differentiation as well as ii) osteoblasts proliferation as well as iii) controlling osteoclast actions. Our concentration is on the actions of variable factors inclusive of i) genetic modifications, ii) environmental pollutants, iii) oxidative stress (OS) iv) mechanical strain along with v) arbitration by pharmacological approaches n Wnt protein modulated events [45]. illustrated that in ankylosing spondylitis, microRNA-96 (miR-96) leads to improvement of osteoblast differentiation as well as bone generation via activation of the Wnt signalling pathway, that got attained by up-regulating the expression of Wnt1,  $\beta$ -catenin, as well as GSK-3 $\beta$ , in addition to stimulated phosphorylation of  $\beta$ -catenin along with GSK-3 $\beta$

activating the WB signalling pathway is attained [45,12,46]. observed that cadmium, in the form of a frequent environmental pollutant, possesses a considerably inimical influence on bone health, particularly cadmium chloride (CdCl<sub>2</sub>), which possesses the capacity of i) diminishing the protein quantities of Wnt-3a, ii)  $\beta$ -catenin, iii) LEF1, as well as iv) TCF in addition to thereby hampering osteogenic differentiation of BMSC's by repressing the WB signalling pathway [46,20]. Additionally, the quantities of Wnt ligand liberated in the body further influences bone generation [47], illustrated that mechanical stress facilitates the gene expression of Wnt ligands, inclusive of i) Wnt1, along with ii) Wnt7b, which escalates the actions of the WB signalling pathway as well as facilitates bone formation [47]. we showed how Wnt 10b was further illustrated by mechanical stress action in [20]. Noticeably, proteins of wingless -related integration site (Wnt) apart from facilitating osteoblast differentiation, further influence osteoclasts. Osteoclasts further express canonical Wnt receptors, as well as [48] observed that Wnt3a possesses the capacity of activating  $\beta$ -catenin signalling in addition to thereby hampering osteoclast differentiation, while Wnt3a further possesses the capacity of hampering osteoclast differentiation through activation cyclic adenosine mono phosphate (AMP/protein kinase A (PKA), that offers expositions for the manner, the proteins of wingless-related integration site (Wnt) shows a double controlling parts in osteoblast as well as osteoclast differentiation [48]. Such observations also highlight the meaningful part possessed by WB signalling pathway in bone physiology WB signalling pathway in bone physiology in addition to yields a significant theoretical ground in reference to generation of therapeutic approaches.

## 2.2 $\beta$ Catenin

$\beta$ -catenin's evolution traces back to a single ancestral gene in early animals, serving dual roles in cell adhesion (like Armadillo in flies) and Wnt signalling for development, with gene duplications later allowing specialization into distinct adhesion and signalling proteins in complex organisms, while its core functions in setting up body axes and tissue patterns remain remarkably conserved across vast metazoan diversity, even evolving new regulatory layers was initially invented in the form of a member of the, as well as was subsequently observed to be a centre member of the Wnt/ $\beta$ -catenin signalling pathway [49].  $\beta$ -catenin is an armadillo family protein encoded by the CTNNB1 gene, that possesses abundance in the N-terminal Ser as well as The in addition to controls the stability of the molecule [50]. I)The C-terminus comprises of 100 amino acids, that activates the transcription of target genes, along with ii) facilitates the beginning as well as expansion of transcription by combining with a cascade of ubiquitous transcription cofactors, for instance i) histone

acetyltransferase in addition to ii) chromatin remodelling factor, etc. 2) The intermediate linker arm is categorized into 12 Arm repeats (R1 ~ R12), along with generates a rod-shaped super-helical structure by the constitution of 12 repeats as well as such structure possesses the capability of efficaciously avoidance of hydrolysis of proteins [51]. The crucial part in reference to the Wnt/ $\beta$ -catenin signalling pathway lies in the existence of stable  $\beta$ -catenin in the cytoplasm, in view of  $\beta$ -catenin is a significant signalling molecule regarding the transmission of Wnt signalling to the nucleus [52]. In the form of a pivotal molecule in the WB signalling pathway,  $\beta$ -catenin has been broadly illustrated to possess a significant working in the generation of variable diseases. Wang et al. observed that the expression of FAT4 was down-regulated in cervical cancer, however FAT4 possesses the capability of binding to  $\beta$ -catenin, causing avoidance of it from entering the nucleus, facilitating  $\beta$ -catenin phosphorylation in addition to breakdown, along with efficaciously hampering the pathological activation of WB signalling pathway. Additionally, by restricting  $\beta$ -catenin activity, FAT4 (FAT4 atypical cadherin 4 alias cadherin family member 14 (CDHF14) or FAT tumour suppressor homolog 4 (FAT4), further possesses the capacity of diminishing the expression of programmed death ligand1 (PDL1) as well as STT3A (STT3A refers to a crucial gene and its protein product, a catalytic subunit of the Oligodactyly, vital for protein N-glycosylation in the endoplasmic reticulum (ER), where sugar chains (glycans) are added to proteins. STT3A (and its counterpart STT3B) forms complexes (OST-A/OST-B) with differing roles, with STT3A mainly handling most proteins co-translationally in addition to cause abnormal glycosylation), along with breakdown of PD-L1, that might be advantageous for the escalation of anti-tumour immune reactions [53,54,55]. isolated the oncogenic part of lnc RNA LINC01226 in gastric cancer, as well as observed that LINC01226 possessed the capability of binding to STIP1 protein, that in turn facilitated the disconnection of STIP1-HSP90 complex. Such event escalated the crosstalk amongst HSP90 as well as  $\beta$ -catenin in addition to stabilized the expression amount of  $\beta$ -catenin protein, therefore facilitating accrual in the cell, along with secondary to that, activated the Wnt/ $\beta$ -catenin signalling pathway, which eventually assisted in the generation of gastric cancer [55,56]. observed that the scaffolding protein namely the receptor for activated C kinase 1 (RACK1) is intricately correlated with tumour generation. Proteasome26S subunit non-ATPase 2 (PSMD2) is an innovative binding chaperone of RACK1 as well as  $\beta$ -catenin. In breast cancer (BC) cells, RACK1 causes avoidance of ubiquitinated  $\beta$ -catenin from binding to PSMD2 to confer protection to it from proteasomal breakdown, thereby stabilizing  $\beta$ -catenin. This facilitates the activation of Wnt/ $\beta$ -catenin signalling as well as the proliferation of cancer cells

[57,58]. illustrated that  $\beta$ -catenin possessed a meaningful part in the generation in addition to propagation of diabetes mellitus (DM), along with colon cancer. DM stimulates the shedding of platelet-endothelial cell adhesion molecule 1 (PECAM-1) from endothelial cells as well as its internalization in addition to agglomeration encompassing the nucleus of the cells, which result in the entry of  $\beta$ -catenin into the nucleus of the cells to facilitates the propagation of colon cancer, along with endothelial mesenchymal transition (End MT) [58]. Further studies are needed to be pursued for gaining insight of the correlation amongst tumours in addition to  $\beta$ -catenin. Additionally, it could be meaningful to deeply evaluate the part of  $\beta$ -catenin in diabetic patients, particularly in association with End MT. Apart from all such observations, studies have documented plausible therapeutic targets as well as strategies, for instance utilization of molecules for instance i) NLRP12 along with ii) FAT4 in reference to controlling the activation of the  $\beta$ -catenin signalling pathway, that might be attractive in reference to generating innovative therapeutic strategies. Greater therapeutic plausibility needs further evaluation with future studies possessing the capability of achieving deeper insight in addition to assessing viewpoint of its implementation in the clinical scenario. Therefore

Recent studies have documented that  $\beta$ -catenin possesses a significant part in skeletal physiology as well as pathology. Skeletal fluorosis, a bone metabolic disease, possesses the properties of exacerbating bone turnover in addition to aberrant osteoblast action [59]. illustrated that fluoride meaningfully i) escalated cancellous bone generation, along with ii) protein expression of a) Wnt3a, b) GSK3b, as well as c) Runx2 in mice; nevertheless, hampering of  $\beta$ -catenin repressed the fluoride-induced Runx2 protein expression in addition to osteogenic phenotype, pointing that  $\beta$ -catenin might be a therapeutic target for skeletal fluorosis [59].

Earlier we had shown butyrate was required for PTH to increase the number of bone marrow (BM) regulatory T cells (Tregs). Tregs stimulated production of the osteogenic Wnt ligand Wnt 10 b by BM CD8<sup>+</sup> T cells, which activated Wnt-dependent bone formation. Together, these data highlight the role that butyrate produced by gut luminal microbiota plays in triggering regulatory pathways, which are critical for the anabolic action of PTH in bone [13]. Conversely, [60,61]. illustrated that the therapeutic activity of PTH is ameliorated in mice with type 1 diabetes, however, once preactivated with  $\beta$ -catenin in osteoblasts escalated the anabolic action of PTH on bone in mice with type 1 diabetes (T1D), meaningfully causing improvement of bone structure, bone volume, along with buttressing of bone [59- 63]. Additionally, [64]. observed

that at the time of skeletal mineralization in mice, the complex generated by the binding of calcium sensing receptor (CaSR) along with Homer1 possesses the capability of activating AKT via mTORC2 in reaction to extracellular calcium ion stimulation, therefore stabilizing  $\beta$ -catenin in osteoblasts, an event's pivotal in facilitating cell differentiation [63]. While, Gupta et al. [65]. observed that Connexin43 (Cx43), in the form of an intercellular communication protein, possesses the capacity of escalating Wnt- based as well as non-Wnt- based  $\beta$ -catenin signalling therefore modulating osteoblast working, bone regeneration, in addition to bone metabolism by overlapping its working with  $\beta$ -catenin [65]. We had displayed the part of Cx43 in ref no 6 Microfibrillar-associated protein 5 (MFAP5) is a constituent of the extracellular matrix (ECM) genes, that possesses a part in the controlling of cell motility, along with signalling, as well as [66]. observed that MFAP5 was capable of facilitating osteoblast differentiation partially via the up-regulation of  $\beta$ -catenin as well as p-GSK-3 $\beta$  to activate the Wnt/ $\beta$ -catenin signalling pathway [66]. Such observations escalate our insight regarding mechanistic modes of  $\beta$ -catenin's part in skeletal physiology in addition to pathological events.

### 2.3 Frizzled receptor (Fzd)

The Fzd receptor delineate a seven-transmembrane protein which is structurally analogous to the G protein-coupled receptor (GPCR). The extracellular N-terminus of the Fzd receptor is a ligand-binding site that binds to Wnt protein, is considerably preserved, as well as is enriched in cysteines [67]. Additionally, the intracellular C-terminus possesses the capability of transmitting signals from the extracellular region to the Dvl, that result in hampering the breakdown of  $\beta$ -catenin as well as thereby controlling the expression of the target gene [68-70]. Fzd proteins are correlated with a i) broad plethora of biological working as well as ii) metabolism, thereby resulting in the beginning in addition to propagation of variable diseases once Fed proteins are impacted. Ding et al. generated a particular alternative to Fzd4, L6-F4-2, that caused improvement of blood-brain barrier (BBB) or blood-retinal barrier (BRB) working by activating the Norrin/Fzd4/TSPAN12 pathway [71]. Such observations possess repercussions for the treatment of i) neurodegenerative diseases (NDD), as well as ii) ocular diseases implicating barrier impairments. Zheng et al. [72]. illustrated that Fzd5 varies from other Fzd proteins in that its preserved extracellular chain site i) binds cholesterol, that in pancreatic ductal adenocarcinoma (PDAC) facilitates the growth of cancer cells through the activation of the Wnt/ $\beta$ -catenin signalling pathway by Fzd5 [72]. Additionally [73]. Observed that ii) elimination of the desert lnc RNA HIDEIN diminishes

the crosstalk's amongst the IMP1 protein in addition to the Fzd5 mRNA therefore by resulting in destabilization of the Fzd5 mRNA, that is imperative for endodermal differentiation [73-75]. illustrated that in prostate cancer, GIPC2 possesses the capability of directly binding to Fzd7 via its PDZ structural domain, which activates the Wnt/ $\beta$ -catenin cascade to facilitate metastasis of prostate cancer cells [74,75]. Noticeably, Fzd6 possesses a significant part in the form of a vital gene in the controlling of tissue polarity [76]. illustrated that knockdown / knockout of Fzd6 in melanoma diminished tumour cell invasion however did not influence proliferation [76]. These studies have illustrated that Fzd proteins are implicated in signalling pathways that influence a plethora of physiological as well as pathological events, inclusive of i) prostate cancer, ii) PDAC, in addition to iii) human endodermal differentiation. Thereby, research on Fed proteins possesses the capability of aiding in further getting greater insight the controlling mechanistic modes of variable diseases as well form innovative drugs targeting Fed proteins, which possesses the capability of offering innovative thoughts in reference to therapies of diseases.

Fzd proteins act in the form of vital members of the Wnt/ $\beta$ -catenin signalling pathway, that is vital for osteoblast working [77]. observed that i) matrix mineralization, ii) expression of osteoblast differentiation markers, along with iii) reactions to Wnt3a were meaningfully ameliorated in osteoblasts possessing deficiencies in Fzd4, as well as furthermore, expression of iv) Fzd8 was escalated in Fzd4- deficiencies possessing osteoblasts, that suggests that there might be certain magnitude of functional overlap between Fzd4 in addition to, Fzd8 [77]. Additionally, fibroblast growth factor (FGF) is believed to possess a significant part in osteoblast differentiation [78]. observed that genes of the Fzd Wnt receptor family (Fzd1, -2, -7, as in addition to -8 genes) which get downregulated by FGF, therefore hampering osteoblast differentiation [78]. Additionally, set al. illustrated that the transcription factor Specificity protein1 (Sp1) possesses the capacity of, controlling the expression of plethora of genes, are inclusive of the ones which are imperative for growth as well as generational events, in addition to that Sp1 possesses the capacity of escalating differentiation as well as mineralization of osteoblasts in vitro via the activation of Fzd1 [79,80]. illustrated that miR-129-5p targets the Fzd4/ $\beta$ -catenin signalling pathway, causes hampering of osteoblast differentiation, along with diminishes osteoblast markers [80]. Taken together Fzd possess a significant part in bone development as well as osteoblast differentiation in addition to, is influenced by a plethora of factors. Thereby, research targeting Fzd may possess greater therapeutic plausibility regarding therapy of skeletal diseases.

2.3 Low-Density Lipoprotein Receptor-Related Protein 5/6 (LRP5/6) LRP5/6 delineates a low-density lipoprotein receptor-related protein, a co-receptor that possesses the properties of a single transmembrane [81]. Additionally, it possesses an i) intracellular site as well as ii) an extracellular site, every one of these possessing variable working [82]. i) The intracellular site possesses the capacity of cross talking with Axin in addition to GSK-3 proteins owing to the possession of PPPS/TPxS/T modules [83,84]. ii) The extracellular domain is further capable of getting categorized into i) the epidermal growth factor structural domain, along with ii) the low-density lipoprotein receptor structural domain, where epidermal growth factor structural domain binding takes place as to Wnt as well as thereby transmits signals [85]. LRP5/6 portray vital co-receptors in the Wnt/ $\beta$ -catenin signalling pathway that possess vital part in variable physiological events in addition to have been implicated in the pathogenesis of various diseases. Borrell-Pages et al. observed that the transcriptional controlling of LRP5 gets influenced by agglomerated low-density lipoprotein (ag LDL), along with that LRP5 is implicated in macrophage lipid uptake in addition to transformation to foam cells, which possess a pivotal part in impacting the initiating along with propagation of atherosclerosis [86,87]. In the meantime [88], illustrated that both lipid uptake by macrophages implicates two molecules, i) LRP5 as well as ii) Protein Convertase Subtilisin/Kexin 9 (PCSK9), in addition to intriguingly, that LRP5 is further involved in the mechanistic modes of PCSK9 liberation [82-89], illustrated that i) LRP5 insufficiency aggravates myocardial ischemic damage, illustrating a protection conferring actions of LRP5. ii) Dkk1, which mirrors a damage hampering agent of the Wnt/ $\beta$ -catenin pathway, escalates the damage reactions by stimulating endocytosis along with breakdown of LRP5/6 [89,90].

Illustrated that the generation of autosomal dominant polycystic kidney disease (ADPKD) is intricately correlated with the LRP5 variant, Fz that has been observed to be implicated in the generation of tubular fibrosis via the direct controlling of the TGF- $\beta$ /Smad signalling pathway [90]. Selen protein P (SELENOP) which possesses the properties of the existence of selenocysteine, that is basically liberated by the liver. Prabhu illustrated that SELENOP is a Wnt signalling controller, that crosstalk's with Wnt3a as well as LRP5/6 to impact colorectal tumorigenesis [91]. Clarification exists from the aforementioned observations that LRP5/6 possesses a significant part in variable diseases. Further studies are needed to be pursued to ascertain the controlling mechanistic modes of LRP5/6. in addition to further evaluate greater targeted therapeutic approaches.

LRP5/6 is an important receptor broadly implicated in the controlling of skeletal cell working, that is vital for bone generation, growth and sustenance of bone density [92]. isolated circRNA422 in rat bone marrow mesenchymal stem cells (BMSC), which possess the capacity of facilitating BMSC proliferation as well as osteogenic differentiation by controlling the expression of SP7 in addition to RP5, along with possesses a promoting action on the early osseointegration events [92-93]. observed that osteogenesis imperfecta (OI) is one of the conditions correlated with LRP, as well as that variants in LRP5 in addition to LRP6 result in the generation of variable types of abnormalities along with conditions for instance i) fracture fragility or ii) oligodontia [93-94]. observed that the Lrp5A214V mutation results in greater bone mass as well as improvement of bone microarchitecture, along with buttressing of bone, in addition to peripheral glucose metabolism, as well as possess the capacity of becoming optimal therapy regarding high risk of fracture in diabetes [94-95]. Illustrated an escalated part of Wnt3a i) in osteoblast proliferation as well as ii) early differentiation, highlighting the significance of LRP6 over LRP5 in modulating ed Wnt3a signalling [93-96]. who observed that LRP5/6 possesses a significant part in mature osteoblasts, as well as that the absence of each possesses an action on bone density in addition to bone structure, with the action of LRP6 being greater prominent, pointing that its part in osteoblasts is greater vital in contrast to that of LRP5 [96]. Future studies are needed to be pursued to ascertain molecular mechanistic modes of LRP5, in addition to LRP6 in skeletal cell biology along with further document their correlation with bone diseases for instance i) fracture healing as well as ii) osteoporosis. In the meantime dependent on deeper insight of LRP5/6, therapeutic strategies possess the capacity of greater evaluation LRP5/6, regarding tackling greater inclusive of generation of innovative drugs as well as therapeutic approaches targeting their signalling pathways regarding tackling in a greater advantageous manner the clinical concerns associated with bone health.

## 2.4 Axin

Axin mirrors a negative governor of the Wnt/ $\beta$ -catenin signalling of the Wnt/ $\beta$ -catenin signalling pathway as well as its binding takes place to variety of members of the Wnt/ $\beta$ -catenin signalling pathway. The N-terminal site is the i) binding site of APC as well as ii) Axin, the middle site possess the capacity of binding i) GSK-3, ii)  $\beta$ -catenin in addition to iii) CK1, along with the 2)C-terminal site is the site where Axin generates homo-oligomers, that is further acknowledged in the form of the DIX structural domain. Axin possesses both Axin1 as well as Axin2 family members in addition to both are structurally analogous

[97]. Axin1 controls the phosphorylation, along with stability of  $\beta$ -catenin by generating complexes with other proteins for instance i) GSK-3 $\beta$ , ii) APC, as well as iii) CK1 [98]. Axin2, despite its expression designs as well as working in cells vary from that of Axin1, possesses a necessary part in embryonic generation, particularly in skeletal generation [99]. Recent studies have illustrated that Axin2 is correlated with a plethora of diseases in addition to tumors correlated with the skeletal system. In recent years, greater as well as greater diseases which possess aberrant expression or mutation of Axin have been isolated, further illustrating the significant part of Axin in disease generation [100]. Study displayed an emphatic cellular contention amongst i) neural progenitor cells (NPCs) at the time of brain generation that possesses the objective of weeding out inappropriate, cells as well as ii) thereby idealization of the organogenesis, an event stimulated by genetic mosaicism of Axin2 in addition to, Trp53 [100], Lysophosphatidic acid (LPA) is an endogenous phospholipid that possesses vital part in the controlling of cellular homeostasis in addition to in the malignant behaviour of cancer cells via G-protein-coupled receptors [101]. observed that LPA facilitates gastric cancer generation as well as propagation, in addition to one of the mechanistic modes was inclusive of LPA possesses the capability of decontrolling energy metabolism via the LPAR2 receptor along with Axin2 [101,102]. observed that RNF146, a RING type E3 ubiquitin ligase, was manipulated by Summarization, that also facilitated its interbedding with Axin, aggravated Axin breakdown as well as escalated Wnt/ $\beta$ -catenin signalling, an event that accounts for the propagation of hepatocellular carcinoma [102-103]. Illustrated that knockdown of Axin2 facilitates mitochondrial biogenesis in addition to, dopaminergic neurogenesis in a rat model of Parkinson's disease, that is attained via manipulation of the Wnt/ $\beta$ -catenin signalling pathway [103]. Aberrant expression of Axin is observed in a range of diseases, further illustrating its significant part in disease phenomenon as well as generation.

Future studies on the working in addition to controlling mechanistic modes of Axin along with evaluation of its particular mechanistic modes in variable diseases would account for further portraying the controlling network of the Wnt/ $\beta$ -catenin signalling pathway in addition to provide an in-depth insight of the unravelling of the mechanistic modes of disease phenomenon. Axin represent 's a significant protein that possesses an important part in a range of cell differentiation along with proliferation events.

In the skeletal system, the association amongst Axin as well as osteoblasts has further got escalated interest. MiR-16-5p represents a miRNA that possesses the capacity of controlling

osteogenic differentiation [104]. illustrated that miR-16-5p in BMSC-obtained extracellular vehicles (EVs) possesses the capability of attaining its working of facilitating osteogenic differentiation by repressing the expression of Axin2, yielding a new mechanistic mode that offers expositions of its significant part in osteogenesis [104-105]. demonstrated that SNPrs9921222, an intronic variant of Axin1 correlated with bone mineral density (BMD), possess the capability of controlling the initiating as well as propagation of bone diseases in human osteoblasts by controlling Axin1 via GATA Binding Protein 4 (GATA4) in addition to oestrogen receptor alpha (E $\alpha$ ) binding [105,106]. observed that deficiencies of the E3 ubiquitin ligase RNF146 results in an escalation of the stability of its substrate Axin1, that leads to impairments in Wnt3 a stimulated activation of  $\beta$ -catenin as well as diminished expression of Fgf 18 in osteoblasts, which further disturbs the events of i) osteoblast proliferation, along with ii) differentiation [106]. Future studies might be capable of attempting to document the fine controlling mechanistic modes of Axin in skeletal system generation as well as diseases, search for the crosstalk amongst novel miRNAs or gene polymorphisms as well as, Axin, in addition to the mechanistic modes of cross-controlling of Axin with other signalling pathways, that might be yielding innovative advent in the diagnosis along with treatment of skeletal system diseases.

## 2.5 Adenomatous Polyposis Coli (APC)

APC proteins portray with their large germane molecular mass, possess the capability of generating working complexes with i) Axin as well as ii) GSK-3, amongst others, to control the protein amount of  $\beta$ -catenin in the cytoplasm [107]. APC contains both i)  $\beta$ -catenin in addition to ii) Axin binding domains[108]. APC is a considerably significant cytoskeletal protein which possesses a vital part in several biological events processes for instance i) cell polarity, ii) signal transduction as well as iii) cell cycle regulation. APC is robustly correlated with the generation in addition to phenomenon of a plethora of diseases inclusive of i) CRC ii) gastric cancer iii) Abnormal brain generation along with iv) Cognitive dysfunction [109]. Observed that H. Pylori infection results in DNA injury in gastric stem in addition to progenitor cells. Nevertheless, DNA injury resulting from H. pylori infection was also greater robust once the APC gene was inactivated, an observation that points to a part for APC in the correlation amongst H. Pylori infection as well as gastric cancer generation [109-110]. Observed that N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG) possessed the capability of stimulating colon cancer cells entering an arresting state analogous to senescent cells, that was associated with diminished amounts of APC proteins, in addition to dissipation

of microtubule organization as well as diminished telomeric DNA [110-111]. Observed that chromosome segregation in cells is intricately associated with the APC gene, as well as that carrying a shortened APC gene leads to aberrant chromosome segregation, in addition to that at the time of mitosis, APC possesses placement to the ends of micro-tubules embedded in kinetochores, along with generates a complex with the checkpoint proteins Bub1 as well as Bub3, whereas experiments have further illustrated that APC is a high-affinity substrate for Bub kinase, further confirming the significant part of APC in mitosis [111-112]. Illustrated that APC possesses a significant part in sustenance of the polarity architecture of radial glia at the time of brain generation, as well as that in the lack of APC, radial glia has deletion of their polarity in addition to reactivity to polarity in sustenance of - signals, resulting in altered cellular working in addition to dysfunctional cortical neuron generation, along with migration [112-113]. Observed that elimination of the APC gene in brain neurons results in plethora of exhaustive intragenerational deficiencies, inclusive of learning as well as memory deficiencies, in addition to autism-like behaviours, along with that deletion of APC in the hippocampus results in escalated density of synaptic spines, changes in synaptic working, as well as correlated alterations in molecular modulations as well as cellular adhesion complexes [113]. Future studies need to carry pursuit of unravelling the particular mechanistic modes of APC in disease generation, particularly in tumors as well as the nervous system, in addition to looking for possible therapeutic strategies.

APC proteins possess a significant controlling part in plethora of biological events, particularly apparently which are vital in controlling bone metabolism as well as osteoblast working. Mielea et al. observed that APC knockout in mouse MSC-like KS483 cells led to upregulation of the Wnt/ $\beta$ -catenin in addition to BMP/Smad signalling pathways however osteogenic differentiation was fully hindered, however the hampering action of APC elimination on cellular differentiation possessed the capability of getting ameliorated by escalating the amount of BMP-7 [114-115]. Observed that genistein, a pronounced soyisoflavon, possesses the capability of facilitating osteoblast differentiation via activation of the Wnt/ $\beta$ -catenin signalling pathway by the mechanistic modes that genistein by promoting the activation of autophagy through the transcription factor EB (TFEB), that contributes in breakdown of APC highlighting the plausible therapeutic plausibility by pharmacological approaches in reference to therapy of bone diseases [115,10].

## 2.6 Glycogen Synthase Kinase 3 (GSK 3)

GSK-3 mirror 's a serine/threonine kinase, amongst the two

structural domains of the C-terminal end of the  $\alpha$ -helix as well as the N-terminal end of the  $\beta$ -fold is the binding pocket ATP ( a homologue of AMP-NP), in addition to this catalytic site basically constituted of amino acid residues for instance the i) Lys85 ii) Thr138 iii) Asp133, along with iv) Gin185 [116]. In the Wnt/ $\beta$ -catenin signalling pathway, mechanistic modes by which GSK-3 possesses a negative controlling part implicates phosphorylating  $\beta$ -catenin to facilitate its breakdown ii) while in the positive controlling of this signalling pathway, GSK-3 serves by phosphorylating LRP6 to facilitate the expression of positive generators [117].

Diseases correlated with GSK-3 portray a field that has illustrated considerable promise. GSK-3 possesses a significant part in cell signalling as well as is implicated in the controlling of a plethora of biological events, inclusive of i) cell proliferation, ii) apoptosis, iii) aerogeneration along with iv) metabolic controlling observed that GSK-3 in cardiomyocytes events, i) possesses a significant part in cardiac homeostasis in addition to total survival as well as ii) that the lack of GSK-3 in cardiomyocytes results in interferences with in mitotic categorization, iii) that eventually results in dilated cardiomyopathy [118-120]. illustrated that the elimination of photoreceptor cells results from retinitis pigmentosa (RP), a group of inherited neurodegenerative diseases (NDD), of the retina, possessed the capability of getting diminished once the GSK-3 hampering agent VP3.15 was used in addition to that visual working was conferred protection, along with that this protection conferring was attained by diminishing the expression of neuroinflammatory markers [120-121]. Illustrated that two innovative small-molecule GSK-3 hampering agents (9-ING-41 as well as 9-ING-87) were efficacious in diminishing the viability of breast cancer cells, in addition to that 9-ING-41 further escalated the effectiveness of the chemotherapeutic drug irinotecan (CPT-11) [121-122]. emphasized that Tumour budding grade III CRC is correlated with enhanced GSK-3 expression quantities as well as escalated PD-L1 expression in tumour cells. Noticeably, hampering of GSK-3 diminished tumour budding through necrotic as well as apoptotic pathways in addition to meaningfully escalated activated immune cells to elevate anti-tumour reactions in contrast to programmed death (PD1) programmed death ligand1 (PDL1) barricading strategies (we had earlier reviewed PD1 /PDL 1 barricading pathways might be used in therapy of ovarian cancers and timecoded therapy for non-small lung cancer (NSCLC) [17,18]. Pointing that GSK-3 is implicated in the controlling of tumour differentiation in CRC, along with in contrast to might be implicated in immune escape mechanistic modes [122]. GSK-3, in the form of a signal-controlling molecule, possesses a significant controlling part in osteoblasts as well as osteoclasts. A study in reference to deeper

understanding of its part in osteoblasts in addition to, osteoclasts is beneficial to greater gaining an advantageous insight of the mechanistic modes of metabolic controlling of bone, along with yielding innovative thoughts as well as approaches for the therapy of associated diseases [123]. observed that the utilization of the GSK-3 hampering agent AR28 once utilized aided in endogenous mesenchymal progenitor cells with osteogenic in addition to adaptogenic plausibility to differentiate towards osteogenesis, however that this facilitation of differentiation occurred at the cost of some degree of adipogenicity [123-124]. observed that osteoclast differentiation was hampered, whereas escalation of osteoblast differentiation occurred once utilization of Li2 CO3 locally in the form of GSK-3 hampering agent, documenting the plausible employment of lithium in the form of GSK-3 hampering agent in the therapy of bone damages [124]. Such observations yield innovative thoughts as well as avenues for gaining insight the mechanistic modes of metabolic controlling of bone in addition to the therapy of associated diseases.

## 2.7 Casein Kinase 1(CK1)

CK1 was one of the initial protein kinases observed to possess serine/threonine protein activity along with is implicated in the controlling of cellular signalling in addition to gene expression [125]. It is broadly distributed in eukaryotes, as well as seven isoforms have been isolated in mammals, inclusive of i)  $\alpha$ , ii)  $\beta$ , iii)  $\gamma$ 1, iv)  $\gamma$ 2, v)  $\gamma$ 3, vi)  $\delta$ , along with vii)  $\epsilon$  [126]. The N-terminal end of CK1 is a considerably preserved structural domain of the kinase, that comprises of 290 amino acid residues, with an extensive variability in the C-terminal end, that differs in length from 40 to 180 amino acids [125]. With the escalating research on CK1, a plethora of diseases correlated with CK1 have been isolated, as well as the part of CK1 in the generation of such diseases has been progressively documented [127]. demonstrated that self-renewal of cancer cells which is autonomous of the milieu gets guided by truncating mutations in RNF43, that causes avoidance of the breakdown of  $\beta$ -catenin by immobilizing CK1 at the cell membrane, resulting in maintenance of the activation of transcription of target genes, pointing that truncating mutations in RNF43 possesses a significant part in the generation of cancer [127,128]. Observed that the survival of multiple myeloma (MM) cells is further intricately associated with CK1, as well as that by hampering CK1 action or diminishing the quantity of CK1, autophagic actions in addition to facilitating apoptosis in multiple myeloma cells is capable of getting lowered, thereby hampering tumour growth, along with survival [128,129]. Showed that nicotinamide facilitated the differentiation of pancreatic progenitor cells by hampering CK1 as well as ROCK, in addition to illustrated that hampering of CK1 $\alpha$ , along with

CK1 $\epsilon$  facilitated the differentiation of pancreatic progenitor cells [129]. In reference to the association amongst CK1 as well as osteoporosis, no directly germane relevant research outcomes have been observed in the literature. Nevertheless, as per the presently acknowledged knowledge, CK1 possesses a significant part in the Wnt/ $\beta$ -catenin signalling pathway, that is intricately associated with the events of i) cell proliferation as well as ii) differentiation, etc. Despite, no clarification is present, that there is an association amongst CK1 in addition to the pathogenesis of osteoporosis, from the facet of its biological parts, we can posit the existence of a wee bit of an association amongst CK1 along with, therefore in the future research can further evaluate the plausible part of CK1 in the pathogenesis of osteoporosis.

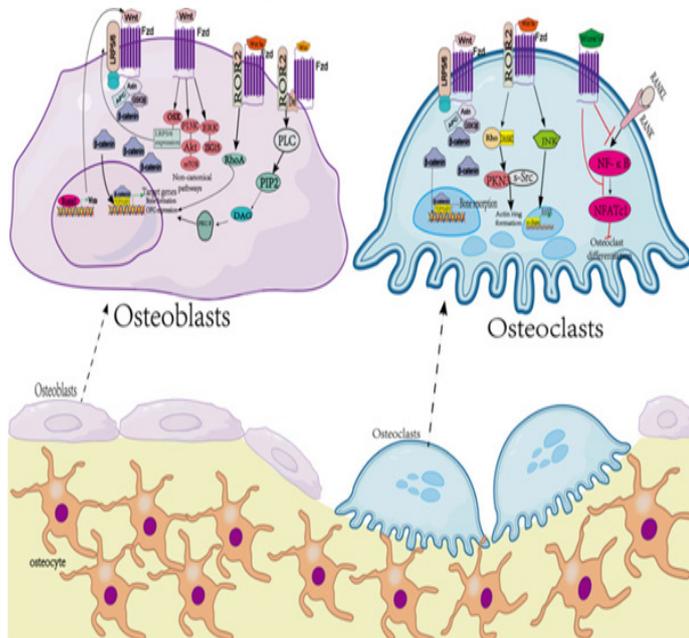
## 2.8 Dishevelled (Dvl)

Dvl delineates a periplasmic protein that is universal in organismal tissue cells as well as is necessary for intracellular transmission of the Wnt/ $\beta$ -catenin signalling pathway. The Dvl protein gets constituted of three main structural domains i) the N-terminus comprises of the DIX site comprising of 51mino acids, ii) the middle portion is the PDZ site that is a primary sequence comprising of 80–90 amino acids, whose existence is amongst greater than 50 proteins for instance i) PSD-95 in addition to ii) ZO-1, along with the C-terminus comprises of DEP site, that possesses the capability of i) binding to the Dvl, ii) EGL10, as well as iii) Pleckstrin proteins [130]. . Dvl protein, in the form of a significant signal- controlling protein, possesses a significant part in the events of i) cell generation, ii) tissue healing, as well as iii) disease generation, in addition to its iv) abnormal working along with controlling disequilibrium are intricately correlated with the phenomenon of plethora of diseases [131]. observed that the expression of ASPM (a novel Wnt coactivator) was gradually up-regulated in basic in addition to metastatic prostate cancer along with that ASPM cross talked with Dvl-3 to hamper the enzyme some- based in addition to escalates the protein stability of Dvl-3, that escalates Wnt -stimulated  $\beta$ -catenin transcriptional actions therefore aiding in the generation of prostate cancer [131,132]. observed that mutations in the Dvl gene were existent in human patients possessing neural tube abnormalities, along with Dandy-Walker malformations, that led to barricading of the Wnt/ $\beta$ -catenin signalling pathway, in addition to the observations that just the Dvl2 p.R633W mutation illustrated greater robust malformations in zebrafish embryos once contrasted to wild-type Dvl2 toxicity, illustrating the significant part of Dvl mutations in the pathogenesis of human neurological diseases [132]. In the skeletal system, Dvl has further been observed to possess a significant part in osteoblast working. The next section will be delving on the controlling part of Dvl in osteoblasts in addition to its significance to the

health of the skeletal system [133]. observed that CXXC finger protein 5 (CXXC5) is a negative feedback governor of the Wnt/ $\beta$ -catenin pathway, that possesses the capacity of hampering osteoblast differentiation in addition to bone generation, along with the major mechanistic modes of this is that CXXC5 evokes a negative feedback actions by binding to Dvl [133]. Isolated a protein also known as ubiquitin-specific enzyme 4 (USP4), that hampers osteoblast differentiation by elimination of the Lysine-63- associated polyubiquitin chain on Dvl generating a hampering action on Wnt/ $\beta$ -catenin signalling [118,119].

### 3. Natural substances

The Wnt/ $\beta$ -catenin signalling pathway is one of the crucial mechanistic modes controlling bone metabolism, that impacts osteogenic actions as well as osteoclast genesis, along with maintains the health in addition to regeneration of bone tissue [134]. None the less, the manner Wnt/ $\beta$ -catenin signalling pathway needs to be modulated regarding preciseness for the therapy of diseases are inclusive of i) Osteoporosis, ii) Fracture as well as iii) Other diseases associated with bone elimination continues to be a main botheration for present scientific researchers. Regarding natural substances that are believed to be valuable regarding escalating in view of their plausible bioactivity in addition to therapeutic plausibility, here a summary of significant natural substances that have been observed to crosstalk with the Wnt/ $\beta$ -catenin signalling pathway, that could be yielding innovative approaches for the therapy treatment of diseases is provided (Fig. 2).



**Legend for Figure2**

Courtesy ref no. 20- Schematic diagram of Wnt signalling-controlling of osteoblasts as well as osteoclasts. In case of osteoblasts,  $\beta$ -catenin- based canonical signalling stimulates

bone generation by facilitating osteoblast genesis in addition to upregulating OPG expression. Non- $\beta$ -catenin based - atypical signalling escalates LRP5/6 expression along with facilitates osteoblast differentiation. iii) runx1 activates Wnt signalling by escalating Wnts expression as well as facilitates osteoblast differentiation. Non- classical Wnt5a signalling via ROR2 activates RhoA, that is imperative in addition to adequate for osteoblast differentiation. Additionally, Wnts further facilitates osteoblast differentiation along with bone generation via PLC/PKC $\delta$  signalling. In case of osteoblasts, canonical Wnt signalling hampers bone resorption, whereas non- canonical Wnt signalling facilitates bone resorption. Wnt5a-ROR2 signalling escalates RANKL- stimulated osteoclast genesis by escalating RANK expression via activation of c-Jun. The Wnt5a-ROR2 signalling pathway activates Rho in an adaptor- based fashion with the aptamer protein Daam2. Following that, the Rho effector kinase Pkn2 activates Rho. Which gets followed by, the Rho effector kinase Pkn3 binding to c-Src as well as facilitates actin ring generation, therefore escalating bone resorption. Wnt4 in addition to Wnt16 hamper RANKL- stimulated activation of NF- $\kappa$ B along with NFATc1 signalling, therefore hampering osteoclast differentiation Abbreviations- LRP5/6 -low-density lipoprotein receptor-related protein5/6; PLC- phospholipase C PKC $\delta$ - protein kinase C, RANKL -receptor activator of nuclear kappa B ligand NF  $\kappa$ B- nuclear factor  $\kappa$ B NFATc1- nuclear factor of activated T cellsc1

A plethora of variable tissues as well as organs for instance the i) myocardium, ii) liver, iii) thyroid, iv) adrenal glands, v) white adipose tissue (WAT), in addition to vi) central nervous system (CNS), liberate a substance also known as irisin, that portrays a muscle obtained- factor, along with gets liberated at the time of exercise [135,136,10,61,63,]. The differentiation of osteoblasts diminishes under microgravity, however [60,62,]. illustrated that irisin facilitates the expression of the osteogenic marker genes i) alkaline phosphatase (Alp), ii) collagen type 1 alpha-1(Coll $\alpha$ 1)), as well as further facilitates osteoblasts differentiation under microgravity by iii) escalating the expression of  $\beta$ -catenin [60,62].

A)Curculio orchioides, delineates a traditional Chinese medicine, possesses the capacity of treating several diseases inclusive of i) bone atrophy, ii) osteoporosis, along with iii) numbness of the limbs [137]. The major bioactive constituents of curculio orchiditis are inclusive of i) polysaccharides, ii) phenolics, nonvolcanic in addition to iii) terpenoids [138]. (COP70-1 is a bioactive ingredient identified from curculio orchioides that facilitates osteoblast differentiation. One of the mechanistic modes delineated is that COP70-1 stimulates GSK-

3 $\beta$  phosphorylation in a quantity - based fashion in therefore escalating the stabilization as well as accrual of  $\beta$ -catenin proteins in addition translocating them to the nucleus, beginning the expression of TCF/LEF-1, that facilitates osteogenesis by modulating the Wnt/ $\beta$ -catenin signalling pathway [138,139]. B) Ginkgolide B (GB) portrays a bioactive ingredient identified as well as purified from Ginkgo biloba. It is broadly utilized for its antitumour in addition to anti-inflammatory actions [140]. has observed that GB possesses hampering actions on prostate cancer [140]. b) [141]. have illustrated that GB facilitates ALP activity as well as mineralization in osteoblasts, in addition to upregulates genes that are landmarks of osteoblast differentiation, for instance i) type 1 collagen (Col I), ii) Runx2, iii) Osterix ((Osx) gene, also known as SP7, encodes a crucial zinc-finger transcription factor essential for bone formation), iv) osteocalcin (OCN), along with v) Oste pontin ( OPN), as well as that the mechanistic modes of this is that GB facilitates differentiation of osteoblasts by escalating the quantity of Ser9 phosphorylation of GSK-3 $\beta$ , upregulating the expression of  $\beta$ -catenin, in addition to activating Wnt/ $\beta$ -catenin signalling [141]. C) Paeonia lacrimiform (PL) is usually utilized to treat a plethora of disorders for instance i) irregular menstruation along with ii) dysmenorrhea, possesses several biological actions, for instance i) anti-inflammatory, ii) anti-cancer, as well as and iii) anti-pigmentation. Albi florin, the major active ingredient in peony, is imperatively a monoterpene glycoside. Albi florin which possesses the capacity of i) avoidance of osteoporosis via antioxidant actions [142]. In addition to further diminishes inflammation in the lungs [143]. Along with resulted in improvement of memory deficiencies [144]. (D) Recently, observed that Albi florin possesses the capacity of facilitating osteoblast differentiation as well as mineralization. Albi florin escalated the protein expression of BMP-2, RUNX2, along with OSTERIX (in addition to the phosphorylation of Smad, that points that it possesses the capacity of triggering bone generation via the BMP-2/Smad signalling pathway. Additionally, it was observed to escalate s the mRNA expression of i) Wnt10b, ii)  $\beta$ -catenin, iii) LRP5 iv) LRP6, v) Dvl2, in addition to vi) cyclin D1, which illustrated that it possesses the capability of triggering i) osteoblast differentiation as well as ii) regeneration via the Wnt/ $\beta$ -catenin signalling pathway [145]. E) 3,5-dicaffeoyl-epi-quinic acid (DCEQA), mirrors a compound extracted from Atriplex gmelina, obtained from chlorogenic acid, along with is biologically active. Anti-obesity as well as UV photoprotective actions of DCEQA have been revealed. Recently [146]. illustrated that therapy of human bone marrow mesenchymal stromal cells (hBM-MSCs) with DCEQA i) facilitated their differentiation to osteoblasts, as well as escalates ALP actions as well as ii) cellular mineralization, in addition to one of the major mechanistic modes of such DCEQA is that it

escalates the quantities of i) Wnt 10a along with ii) Axin proteins, in addition to phosphorylation of  $\beta$ -catenin, that facilitates the Wnt/ $\beta$ -catenin signalling pathway as well as therefore escalates osteoblasts' differentiation [146]. F) Euodia Sichuanese Dode (ESD) is an ornamental tree species which escalates in temperate areas. ESD possesses a high medicinal action, i) aiding in giving relief to headaches, ii) gastritis in addition to iii) dermatitis, as well as the iv) anti-Mold actions of the geranyl furanocoumarins in its fruits [147,148]. Recently, Hwang et al [149]. revealed that obtained ESD extract might possess therapeutic plausibility for the i) therapy of osteoporosis. They revealed that ESD extract obtained, possesses the capacity of escalating the i) ALP actions as well as ii) mineralization capability of osteoblasts, in addition to that the expression of osteoblast differentiation marker genes, for instance i) Bone morphogenetic proteins (BMP2) , ii) Runt-related transcription factor 2 (RUNX2) along with iii ) COL1A1, were escalated subsequent to therapy as well as that the mechanistic modes were that ESD extract escalated  $\beta$ -catenin quantities in osteoblasts, therefore activating the Wnt/ $\beta$ -catenin signalling pathway [149].

G) Geraniin delineates a substance which possesses a broad variety of biological actions extracted from Phyllanthus Amarus, that is imperatively a cyclic tannin. Geraniin possesses broad variety of i) anti-inflammatory, ii) antioxidant, iii) anti-infectious, iv) antitumour, v) anti-hyperglycaemic as well as vi) anti-hypertensive characteristics [150-155]. illustrated that Geraniin further possesses a facilitating action on the differentiation in addition to proliferation of osteoblasts. Geraniin therapy escalated the expression of a cascade of proteins associated with the Wnt/ $\beta$ -catenin pathway (inclusive of i)  $\beta$ -catenin, ii) Fzd2, iii) LRP6, etc., iv) whereas hampering the expression of Axin2 [155]. Such observations indicate that Geraniin might escalate osteoblast working by activating the Wnt/ $\beta$ -catenin pathway.

H) Astragalus portrays a Chinese herb with a range of biological actions inclusive of i) anticancer, ii) anti-inflammatory, along with iii) antioxidant. What is intriguing is that astragalus possesses the capacity of hampering bone elimination in ovariectomized mice [156,157]. Observed that As-I stimulated osteoblast differentiation, escalated ALP activity as well as its mineralization capacity, in addition to the major mechanistic modes were that As-I escalated the expression of  $\beta$ -catenin, along with Runx2 proteins therefore escalating the Wnt/ $\beta$ -catenin signalling pathway [157].

I) Bergamottin (BM), a natural substance, is basically extracted from a plethora of citrus fruits. It possesses several biological actions, inclusive of i) anti-adipogenesis, ii) antioxidant as

well as iii) anti-cancer [158,159]. Recently, observed that BM possessed the capability of controlling the Wnt/ $\beta$ -catenin signalling pathway by escalating the expression of LRP6, Wnt3a as well as  $\beta$ -catenin in addition to diminishing the expression of GSK-3 $\beta$  to facilitate osteoblasts differentiation ameliorating the elimination of bone mass along with resulting in improvement of bone turnover in OVX-stimulated osteoporosis in mice [74,75].

J) Psidium guajava has been observed to possess an important effectiveness in diminishing down a number of metabolic diseases for instance i) diabetes, ii) obesity as well as iii) osteoporosis [160]. Porwal et al. [161]. identified i) gallic acid, ii) agriolimacids (UA), iii) 2 $\alpha$ -hydroxyursolic acid (2 $\alpha$ -UA), iv)  $\beta$ -sitosterol as well as v)  $\beta$ -sitosterol-D-glucoside from guava extract (GE). Among them, just UA in addition to 2 $\alpha$ -UA escalated ALP actions, along with the mineralization capability of osteoblasts, in addition to the major mechanistic modes was that 2 $\alpha$ -UA possessed the capability of up-regulating the RNA quantities of Runx2, along with Wnt3a, while UA possessed the capability of escalating the quantities of BMP-2, Col1 to as well as Wnt3a in osteoblasts, therefore escalating the Wnt/ $\beta$ -catenin signalling pathway [161,14,20].

K) Gigas delineates a nutrient-rich food. Fermented Oyster Extract (FO) is enriched in protein as well as carbohydrates. Additionally, lysine in addition to GABA possess the maximum enrichment of amino acids in FO. Such nutrients might possess a significant part in human health in addition to bone generation [162]. observed that FO facilitated osteoblast differentiation, along with escalated the expression of particular marker proteins for instance i) RUNX2, ii) ALP, iii) Col1 $\alpha$ 1, iv) OCN, v) OSX, as well as vi) BMP4, in addition to escalated osteoblast ALP activity along with mineralization capability. One of the mechanistic modes is the capacity of FO to importantly escalate the expression of  $\beta$ -catenin, that activates the Wnt/ $\beta$ -catenin signalling pathway [162,20], This is significant for facilitating osteogenesis as well as sustenance of bone health.

L) Polygonum tibeticum polysaccharide (PSP) mirror 's a compound extracted from the traditional Chinese medicine Polygonum suberic. It possessed a variety of biological actions, inclusive of i) anti-inflammatory in addition to ii) ameliorating amyloid- $\beta$ -induced neurotoxicity [163,164], observed that PSP possessed the capability of facilitating the differentiation of BMSC to osteoblasts, along with escalated the ALP actions as well as mineralization capability of osteoblasts. Additionally, PSP escalated the expression of osteogenic differentiation genes inclusive of i) COL I, ii) ALP, iii) Runx2 in addition to iv) OCN. The major mechanistic mode is that PSP escalate the expression

along with activation of  $\beta$ -catenin, facilitating the accrual of  $\beta$ -catenin in the nucleus which gets followed by cross talking with the transcription factor TCF/LEF to activate the Wnt/ $\beta$ -catenin signalling pathway, therefore facilitating osteoblast genesis as well as working [164].

M) Soybean isoflavones (SI) portray a class of natural compounds observed in soybeans which belong to the isoflavones group. SI mainly are inclusive of i) soy glycosides, ii) soy glycosides in addition to soy brassicas, that are believed to be phytoestrogens, along with possess the capacity of simulating the actions of oestrogen [165]. Studies have illustrated that SI possess a plethora of biological actions inclusive of i) antioxidant, ii) anti-inflammatory, iii) anti-tumour, iv) lipid-diminishing as well as v) improvement of bone density [166], illustrated that SI possesses the capability of i) facilitating osteoblast differentiation in addition to ii) escalate osteoblast ALP actions, along with iii) its mineralization capability, the major mechanistic mode of which is that an escalating quantities of soy isoflavones possess the capacity of escalating the expression quantity of i) Wnt3a, ii) Wnt7b, as well as iii)  $\beta$ -catenin proteins in addition to iv) activate the Wnt3a/ $\beta$ -catenin signalling pathway [166].

N) Arbutin, delineates a natural substance compound extracted from a plethora of plants inclusive of, i) bearberry leaves, ii) pears, in addition to iii) marjoram [167]. is a natural hydroquinone derivative? Arbutin possesses several biological actions inclusive of, i) whitening, ii) anti-inflammatory as well as iii) illustrated that they possessed protection conferring actions against oxidative stress [168,169]. Man et al. [170]. observed that arbutin facilitates promotes osteoblast differentiation as well as escalates ALP actions in addition to, its mineralization capacity, the major mechanistic modes of which is that arbutin significantly escalates the protein expression levels of Runx2 a along with  $\beta$ -catenin, therefore facilitating osteoblast differentiation via the canonical Wnt/ $\beta$ -catenin pathway [170].

O) Kir enol portray 's a natural substance identified from Herba Siegesbeckia, inclusive of, i) S. orientalis, S. glabrescens, as well as S. pubescens, in addition to is a diterpene substance [171]. Kir enol has biological actions with i) antioxidant, ii) anti-inflammatory, iii) anti-allergic, iv) anti-adaptogenic, along with v) anti-arthritic characteristics [171-174]. illustrated that Kir enol possesses the capacity of facilitating osteoblast differentiation as well as escalating the ALP actions in addition to mineralization capability of osteoblasts, in addition to one of the major mechanistic mode is that Kieron escalates the mRNA expression of i) LRP5, ii) Dvl2, iii)  $\beta$ -catenin, along with iv) CCND1 genes, followed by v) up-regulating the actions of Wnt/

P)Cajanus Cajan (L)Millsp. mirror 's a traditional Chinese herb whose fresh leaves are utilized in reference to therapy of a range of ailments inclusive of, i) parasitic diseases, ii) oxidative damage, as well as iii) cancer [175-176]. observed that Cajan lactone A (CLA), a stilbene extracted from Cajanus Cajan (L) Millsp, possesses a facilitating action on osteoblast differentiation, as well as that the major mechanistic mode is that it possesses the capacity of meaningfully upregulating the mRNA quantities of i) Wnt3a, ii) Wnt10b, iii) LRP5, iv) Frizzled 4, v)  $\beta$ -catenin, vi) Runx2, in addition to vii) Osterix, pointing that CLA facilitates osteoblast differentiation by triggering Wnt/ $\beta$ -catenin signalling pathway[176]. (Liu et al. 2019).

#### 4. Conclusions

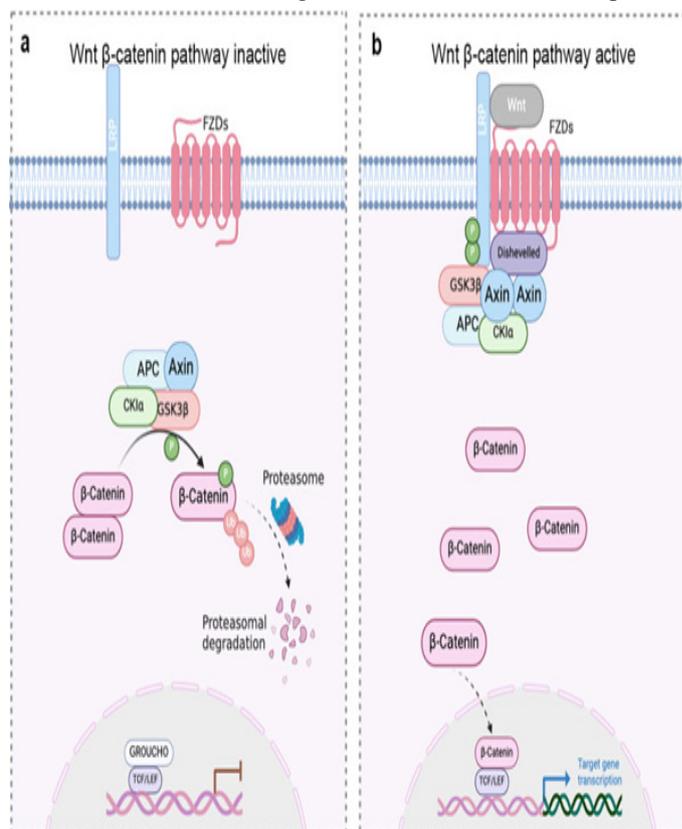
With the escalating acquisition of getting insight in reference to the Wnt/ $\beta$ -catenin signalling pathway, it has been observed that changes in variable proteins in the pathway possess the capacity of resulting in disease sequelae for instance i) cancer, ii) osteoporosis, as well as iii) dysplasia. The Wnt/ $\beta$ -catenin signalling pathway has been acknowledged to possess a vital part in osteoblast differentiation in addition to bone generation. Controlling of such pathway, possesses the capability of facilitating such bone generation, escalating BMD bone mineral density, along with diminishing the fracture risk. Targeted therapeutic regimens against the Wnt/ $\beta$ -catenin signalling pathway have corroborated to be attractive strategies for therapy of diseases. Clinically, therapeutic approaches targeting this pathway, particularly small molecule drugs as well as natural compounds, have illustrated promising therapeutic actions, that possesses the capability of yielding innovative therapeutic modalities for therapies of patients with osteoporosis, in reference to improvement of the QOL of patients, in addition to diminishes the disability, along with complications resulting due to osteoporosis. It is anticipated that future studies be conducted as well as efficacious therapies revolving around the Wnt/ $\beta$ -catenin signalling pathway have been isolated.

In reference to cancer therapy, the aberrant activation of Wnt/ $\beta$ -catenin signalling pathway is intricately associated with the phenomenon in addition to generation of a plethora of cancers. Clarifying the particular mechanistic modes of such pathway in variable cancers would allow for forming particular targeted therapeutic drugs. By hampering the over-activation of such pathway, the proliferation, invasion, along with would be capable of avoidance of metastasis of cancer cells as well as the improvement of actions of cancer therapy can be attained. Additionally, In addition, gene modification in addition to other

technologies also provide innovative new ideas, along with methods for the precision therapy of cancer.

Furthermore, recently [177]. detailed how Frizzled receptors (FZDs) that held responsible for belligerent carcinoma phenotype in Wnt signalling alone might be targeted in the form of plausible therapeutic targets by targeting both canonical in addition to other noncanonical pathways (PCP pathway) for treating human cancers where their concentration was on status of FZD receptors (FZD1-10) along with the current biological classes of small molecule-based FZD hampering agents in depth [177]. (seeFigure3 &4).

Additionally [178]. detailed the manner Natural Bioactive Compounds Targeting the Wnt/ $\beta$ -Catenin Pathway could further escalates the anti-cancer for the Treatment of Hepatocellular Carcinoma Natural synergize with sorafenib to escalate its anti-cancer actions on combining with Natural Bioactive Compounds.

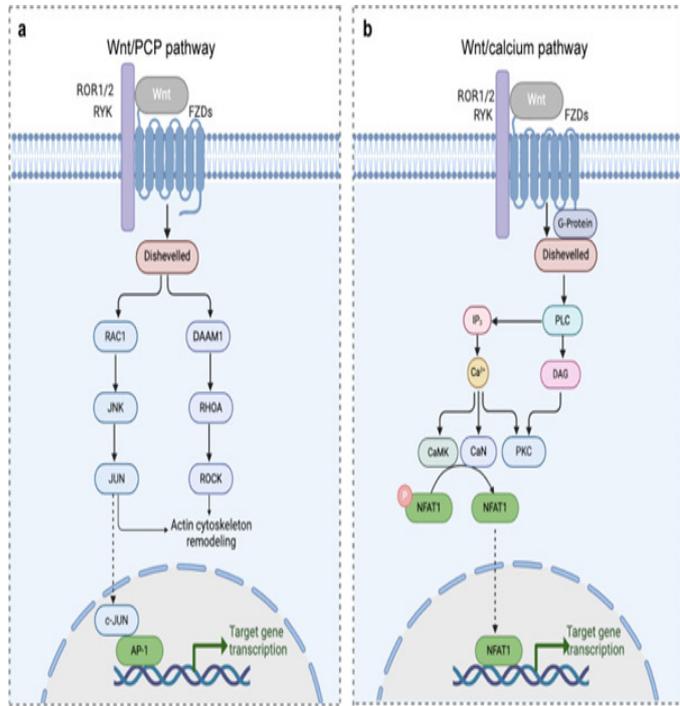


**Canonical Wnt/FZD signal transduction**

#### Legend for Figure3

Courtesy ref no177 - (Created with BioRender.com). a in the absence of the extracellular Wnt ligands, the signalling switch is not activated. Then  $\beta$ -catenin is continuously phosphorylated and degraded, Casein kinase 1 $\alpha$  (CK1 $\alpha$ ), axis inhibition protein (AXIN), adenomatous polyposis coli (APC), and the serine/threonine kinase glycogen synthase kinase3 $\beta$  (GSK3 $\beta$ ) together form the  $\beta$ -catenin degradation complex. Phosphorylation of

$\beta$ -catenin by the degradation complex will further trigger its degradation, thus preventing the abnormal cellular responses triggered by the canonical pathway. b In the presence of Wnt, it binds to two coreceptors on the cell membrane and the degradation complex is inhibited. Free  $\beta$ -catenin is no longer phosphorylated and accumulates in the cytoplasm, then they are translocated to the nucleus to promote transcription of downstream target genes.



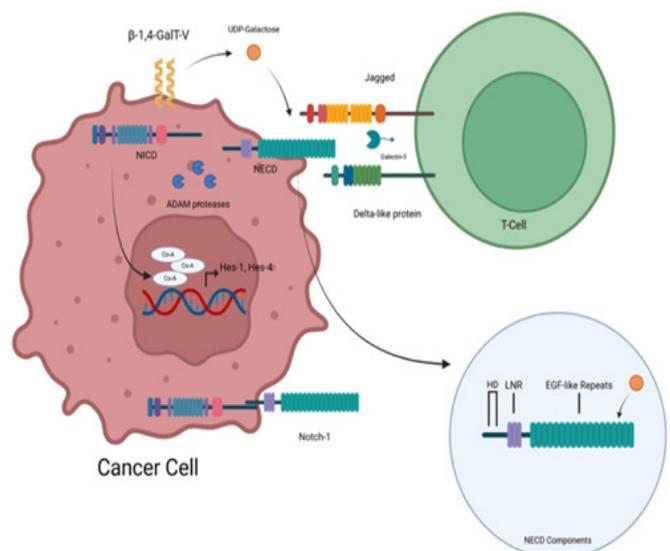
Non-canonical WNT pathways

Legend for Figure4

Courtesy ref no177 - (Created with BioRender.com). a In the Wnt/PCP pathway, the binding of Wnt to FZD and the coreceptor tyrosine kinase-like receptor alone 1/2 (ROR1/2)/receptor-associated tyrosinase (RYK) coreceptor causes the activation of DVL recruitment. The binding of DVL to DAMM1 activates Rho-associated protein kinase and ultimately cause actin skeleton alterations and rearrangements. The activation of DVL can also initiate the JNK signalling cascade by triggering RAC. Then the activation of c-Jun further promotes activator protein 1 (AP-1)-dependent gene transcription, which ultimately regulates cytoskeletal remodeling and cell adhesion. b The Wnt/Ca<sup>2+</sup> cascade activates phospholipase C (PLC) via heterotrimeric G proteins to generate diacylglycerol and inositol 1,4,5-trisphosphate-3 (IP<sub>3</sub>), followed by an increase in cytoplasmic Ca<sup>2+</sup> concentration. The accumulation of Ca<sup>2+</sup> activates Ca<sup>2+</sup>-sensitive enzymes such as calcium-regulated protein kinase II (CaMKII) and protein kinase C (PKC), and calcium activation of CaMKII and CaN dephosphorylates nuclear factor of transcription factor-activated T cells (NFAT),

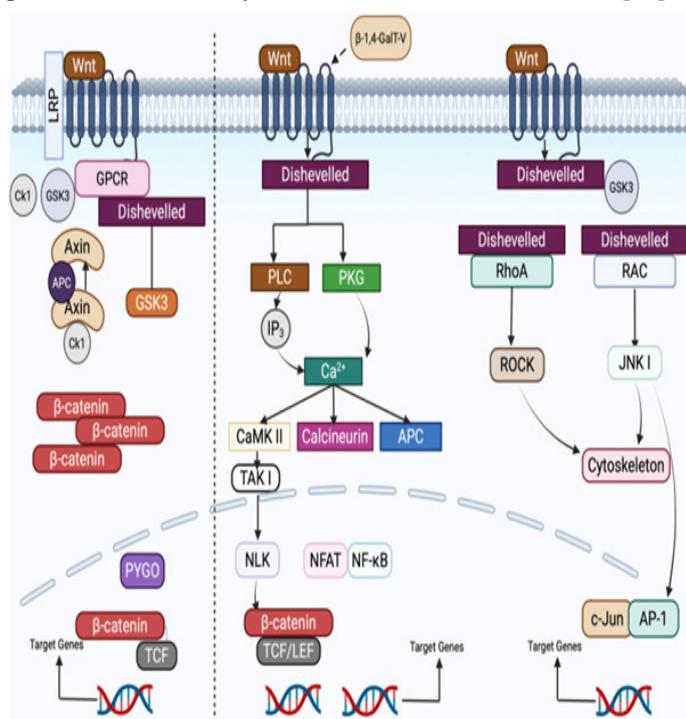
leading to their nuclear import and subsequent NFAT-mediated gene expression

Earlier we have detailed extensively classification of variable kinds of Notch ligands. Additionally, this Notch signalling pathway controls cell-cell communication via transmembrane ligands as well as receptors. The canonical pathway represents 5 canonical Notch ligands namely  $\Delta$ -like canonical Notch ligand (DLL), DLL3, DLL4, Jagged 1 and Jagged 2, along with the 4 receptor paralogs. Different Notch receptors and ligands get expressed via cancer cells, further the non-canonical pathway might also have the same role in cancer. OX2 might be a key factor in self renewal, pluripotency [35,179]. further extrapolated how UDP-Gal- $\beta$ -1,4 galactosyltransferase-V (GalT-V) mirror 's whose working is to transfer galactose from the nucleotide sugar UDP-galactose to a glycosphingolipid glucosylceramide, to form glucosylceramide (LacCer). Its further results in the N as well as O glycosylation of proteins in the Trans Golgi region. LacCer is a bioactive lipid second messenger that activates an "oxidative stress pathway", that results in crucial phenotypes, e.g., cell proliferation, migration angiogenesis, autophagy, in addition to apoptosis. It further activates an "inflammatory pathway" that accounts for the propagation of disease pathology.  $\beta$ -1,4-GalT-V gene expression is controlled by the binding of the transcription factor Sp-1, one of the maximum O-Gluciated nuclear factors. They further described part of the Sp-1/GalT-V axis in disease phenotypes as well as therapeutic approaches targeting apart from Sp-1 but further i) Notch-1, ii) Wnt-1 frizzled, iii) hedgehog, in addition to iv)  $\beta$ -catenin, that is parts of Wnt/ $\beta$ -catenin signalling pathway aid in apart from tackling cancer further possess the capacity of treating]. Cardiovascular disease (CVD) in addition to inflammatory diseases [179]. (seeFigure5-7).



Legend for Figure 5.

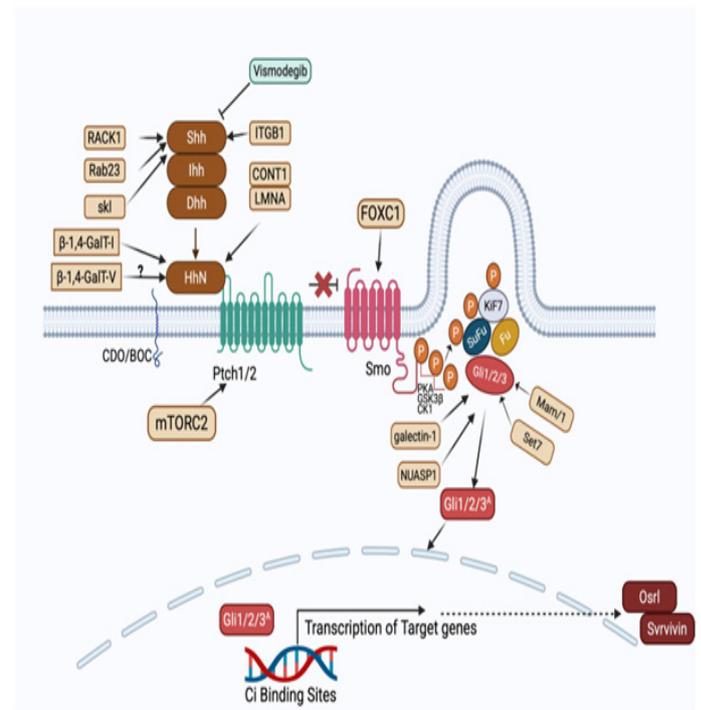
Courtesy ref no-179- -GalT-V- modulated glycosylation of Notch-1 in endothelial cells. Schematic representation of  $\beta$ -1,4-Galactosyltransferase V ( $\beta$ -1,4-GalT-V)- modulated glycosylation of Notch-1 as well as its role in T-cell-cancer cell crosstalk through the Notch signalling pathway. In the cancer cell, Notch-1 is generated in addition to its insertion takes place into the plasma membrane  $\beta$ -1,4-GalT-V makes utilization of UDP-galactose in order to glycosylate the extracellular domain of Notch-1, specifically at the epidermal growth factor (EGF)-like repeats, the manner illustrated in the magnified NECD constituents inset (emphasizing HD: heterodimerization domain; LNR: Lin12/Notch repeats; along with EGF-like repeats). Such glycosylation facilitates crosstalk of Notch-1 with T-cell- obtained ligands for instance Jagged along with Delta-like proteins, whose stabilization takes place further by binding Galectin-3. Cleavage of Notch-1 by ADAM proteases gets stimulated by ligand binding, that causes liberation of the Notch intracellular domain (NICD), whose translocation takes place to the nucleus. NICD crosstalk's with transcriptional co-activators (Co-A) to stimulated the expression of Notch target genes, inclusive of Hes-1 as well as Hes-4. The figure summarizes pivotal molecular constituents implicated in the Notch signalling axis between T-cells in addition to cancer cells, inclusive of,  $\beta$ -1,4-GalT-V, UDP-galactose, Galectin-3, Notch ligands (Jagged, Delta-like) along with the modular domains of the Notch extracellular domain (NECD). Created with permission from Hideyuki Takeuchi and with Bio render [75].



Legend for Figure 6

Courtesy ref no-179- Schematic Illustration of the canonical

as well as non-canonical Wnt pathways delineating tumour propagation. In the case of lack of Wnt ligands, phosphorylation of cytoplasmic  $\beta$ -catenin takes place by a destruction complex constituted of GSK3, casein kinase I (CK1), Axin, in addition to APC. Following that, phosphorylated  $\beta$ -catenin targeting takes place for proteasomal breakdown. Once binding of Wnt ligand to the Frizzled-Lipoprotein Receptor-Related Protein (LRP) receptor complex takes place, it leads to enrolment of Dishevelled (Dvl), resulting in hampering of the  $\beta$ -catenin disturbance complex. This contributes to accrual of cytoplasmic  $\beta$ -catenin which gets followed by translocation into the nucleus, where in partnership with TCF/LEF it guides the transcription of Wnt target genes - classical Wnt/ $\beta$ -catenin pathway). Additionally, Wnt possesses the capability of activating non-classical pathways: for instance, i) the Wnt/ $Ca^{2+}$  pathway, that implicates PLC, PKG, along with  $Ca^{2+}$ - based dependent effectors for instance a) CaMKII, b) calcineurin, as well as c) NFAT; in addition to ii) the planar cell polarity (PCP) pathway, where Dvl activates small GTPases (RhoA along with Rac), resulting in cytoskeletal remodelling via ROCK as well as and JNK. Noticeably,  $\beta$ -1,4-Galactosyltransferase-V ( $\beta$ -1,4-GalT-V) might impact Wnt signalling by modulating Wnt ligand crosstalk. Created with BioRender.com. Taken with Permission from Ref [86].



Legend for Figure 7

Courtesy ref no-179- The binding of Hedgehog ligands (Sonic Hedgehog (Shh), Indian Hedgehog (Ihh), or Desert Hedgehog (Dhh)) to the Patched receptors (Ptch1/2) allows for imparting relief from their repression of Smoothened (Smo), that

contributes to phosphorylation of plethora of Ser/Thr residues at the C-terminus of Smo. This activates Smo as well as stimulates a cytoplasmic signalling cascade implicating Kinesin Family Member 7 (KIF7), Suppressor of Fused (Sufu), in addition to other factors, leading to the nuclear translocation of Gli transcription factors (Gli1/2/3), along with the transcription of downstream target genes for instance *Osr1* and *Survivin*. Governor for instance  $\beta$ -1,4-Galactosyltransferase I ( $\beta$ -1,4-GalT-I) facilitates pathway activation via galactose transfer, as well as  $\beta$ -1,4-GalT-V is posited to possess a comparable part. Other manipulators are inclusive of i) mTOR complex 2 (mTORC2), ii) Forehead box C1 (FOXC1), in addition to iii) membrane-associated proteins for instance a) integrin  $\beta$ 1 (ITGB1), b) Lamin A/C (LMNA), along with c) CONT1. The small-molecule Smo hampering agent vismodegib blocks pathway activation as well as downstream actions (created with Bio Render).

Subsequent to reviewing anatomy of the human skeleton & factors modifying its development/regeneration, therapeutic application of Gut Microbiota & metabolites & avoidance & treating Osteoarthritis & bone associated diseases, pharmacological as well as non-pharmacological fracture risk management for optimizing fractures prevention in potential osteoporotic women (Post menopausal and peri menopausal women [10,11,12,20] & part of herbs in dm avoidance like *Moringa Olivera* (MO) stimulates hepatocyte nuclear factor 4 alpha (HNF- $\alpha$ ) [180], that influences PPAR-1 $\alpha$  to cause blockade of the gluconeogenesis & how in CKD crosstalk of GM, WB, & other pathways affect bone osteoporosis [181]. several modes of cancer avoidance & therapy (howl Nc RNAsCYTOR markedly expressed in CRC controls  $\beta$ -catenin and colon cancer metastasis [15-18,40]. The manner corroborated by earlier studies ER $\beta$  was foresighted as an anticipator regarding BC survival. E2/ ER $\beta$  modulated hostility and stemness characteristics in BC might be partially reasoned out by downstream actions, which facilitate EGFR, vascular endothelial growth factors (VEGF), amphiregulin, wingless-related integration site (WNT) Wnt-10 $\beta$  liberation [182]. here our objective of this review is to provides a summary of the action of Wnt/ $\beta$ -catenin signalling pathway on osteoblast differentiation as well as the association amongst the associated proteins in the pathway in addition to human diseases. Simultaneously, the latest propagation of work on natural substances targeting Wnt/BC signalling pathway against osteoporosis is described. In conclusion, the deep study of Wnt/BC signalling pathway yields innovative trajectories in addition to evokes optimism for the treatment of diseases for instance osteoporosis along with cancer, that possesses significance in clinical scenario. Nevertheless, deeper understanding needs

to assessment chiasitic modes of such pathway in reference to generating novel therapies.

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