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Pharmacological applications of diacerein: A review

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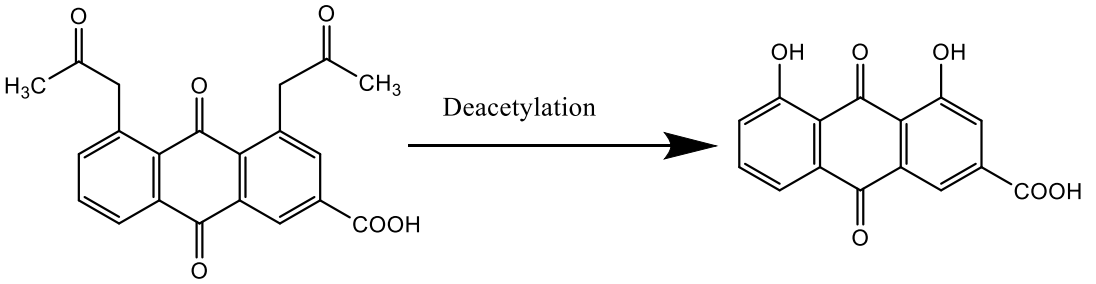
***Abstract*---**IL-1β is one of the important IL-1 superfamily cytokines that shows crucial role in the pathogenesis of various inflammatory disorders like osteoarthritis, epidermolysis bullosa, psoriasis and type II diabetes. Dugs with IL-1βinhibitory effect can show promising results in these types of inflammatory disorders. Diacerein and its active metabolite rhein prevent the generation of active IL-1 and are consequently used to treat inflammatory conditions such as osteoarthritis, epidermolysis bullosa, psoriasis, and Type II diabetes.

***Keywords*---**Diacerein, IL-1β, osteoarthritis, epidermolysis bullosa, psoriasis, Type II diabetes.

Introduction

Diacerein (DCN) is an anthraquinone derivative found in the Cassia gender plant with anti-inflammatory, analgesic, and antipyretic properties [1]. It is known as 4,5-diacetyloxy-9,10-dioxo-anthracene-2-carboxylic acid in the International Union of Pure and Applied Chemistry [1].

It was first synthesised in the 1980s and began to be sold as a tablet in 1994 in various Asian and European countries. Because of its inhibitory action on proinflammatory cytokines including IL-6 and IL-1, it was licenced by the FDA in 2008 for the treatment of osteoarthritis. Along with its tremendous potential in the management of osteoarthritis, its various applications are being researched on a regular basis, including in epidermolysis bullosa, psoriasis, type 2 diabetes, breast cancer and periodontitis [2]. DCN is a kind of prodrug. It is converted to the energetic metabolite rhein via the deacetylation mechanism [2].



Diacerein
(Molecular weight = 368)

Rhein
(Molecular weight = 284)

DCN is entirely converted to rhein before reaching the systemic circulation. Rhein is eliminated primarily through the kidneys (20%) or conjugated in the liver to generate rhein glucuronide (60%) and rheinsulfate (20%), Both of these substances are mostly eliminated via the kidneys [2].

DCN and its active metabolite rhein works by blocking the action of IL-1β, a protein involved in the inflammation. Apart from the IL-1Beta inhibitory effect, diacerein and rhein also reduces the expression of matrix metalloproteinase-1(MMP-1) and matrix metalloproteinase-3 (MMP-3). It plays a crucial part in the treatment of osteoarthritis. Apart from this, it is also having important role in the management of breast cancer, epidermolysis bullosa, psoriasis, periodontitis and type II diabetes [3].

Role of IL-1B in the pathophysiology of osteoarthritis and beneficial roles diacerein in osteoarthritis

The term “Osteoarthritis” originates from Greek words Osteon" which implies the bone, "Arthon" stands for joint and “itis" indicates inflammation [4]. This is the most prevalent type of arthritis that effects older peoples and is considered as degenerative arthritis. It is a kind of arthritis that leads old people to become disabled. Osteoarthritis (OA) is the most prevalent chronic irreversible disorder that effects joints. Obesity, aging, trauma, genetic predisposition plays a dominant role in the pathogenesis of OA. In accordance with latest medical knowledge, immune system plays a crucial role in the pathophysiology and progression of OA. During the advancement of OA, various pro-inflammatory and anti-inflammatory cytokines are expressed which having important role in the development of OA. The group of various proinflammatory cytokines like IL-1β, IL-6, IL-15, IL-17, IL-18 and TNF-α having povital role in the

development of OA. These cytokines involved in stimulation of various catabolic process which ultimately responsible for articular cartilage destruction.
IL-1β is a crucial proinflammatory cytokine that plays a dominant role in the early onset of OA. It stimulates the inflammatory reactions in OA directly along with collaboration with other proinflammatory cytokines. Apart from the activated macrophages, activated chondrocytes, mononuclear cells and synoviocytes also releases IL-1β. Cartilage and subchondral bone of OA patient also express increased level of IL-1β [5,6]. Initially, IL-1β is produced as precursor protein known as pro-IL-1β consisting of 269 amino acids [7,8]. Caspase 1 (IL-1 β converting enzyme or ICE) causes proteolysis of pro-IL-1β to produce active IL-1β with 153 amino acid sequence that is released into extracellular space [9]. Binding of IL-1β to IL-1R1 receptor results in increased expression of various adhesion molecules, chemokines, cytokines, enzymes, & various inflammatory mediators [10]. In normal chondrocytes and OA chondrocytes, IL-1β promotes the production of matrix metalloproteinases (MMPs) like MMP-1, MMP-3, and MMP-13 [11]. These MMPs increases the breakdown of various types of cartilages in osteoarthritic joints.Apart from the stimulation of MMPs, IL-1β increases the expression of ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) like ADAMTS-4 and ADAMT-5 in normal human chondrocytes and OA chondrocyte that responsible for breakdown of aggrecans[11]. (Fig 1).

Apart from increased catabolic effects on cartilage, IL-1β also shows decreased anabolic effects on chondrocytes and cartilage. Various report indicates that IL-1β causes 40% reduction of aggrecan mRNA expression in OA patients [12]. IL-1β treatment causes time dependent reduction in proteoglycan (PG) synthesis and accumulation in rat femoral explants [13]. The inhibitory effect of IL-1β on PG biosynthesis is mainly due to inhibition of galactose- β1,3-glucuronosyltransferase I (GlcAT-1), the main enzyme required for the biogenesis of core protein of PG known as glycosaminoglycan. Apart from its decreased anabolic effect on aggrecan and PG, IL-1β shows its decreased anabolic effects on collagen, the major protein of articular joints. Human chondrocyte cells treated with IL-1β results in decreased expression of type II collagen [14]. Apoptosis of chondrocytes also stimulated by IL-1β.

DCN decreases biosynthesis of IL-1β by inhibiting the enzyme Caspase 1 (IL-1 β converting enzyme or ICE) [15]. All pathologic reactions that lead to OA articular cartilage degradation are improved as a result of this. Apart from IL-1β inhibitory effect, TGF-1 and TGF-2 expression is increased by DCN, which is important for cartilage growth and structure maintenance. DCN inhibits the production of pro-inflammatory cytokines, adhesion molecules, and enzymes by inhibiting IL-1-mediated activation of NF-KB and activator protein-1 (AP-1) transcription factors. It reduces the expression of IL-1 receptors on the surface of chondrocytes [16], while increasing the expression of IL-1 receptor antagonist in an indirect manner [17]. (Fig 2). DCN also reduces IL-1-mediated inducible nitric oxide synthase (iNOS) and NO generation, resulting in reduced chondrocyte apoptosis because NO is thought to play a part in chondrocyte apoptosis [18]. For non-acute treatment, symptomatic slow-acting medicines for OA (SYSADOAs) such as glucosamine, chondroitin sulphate, and diacerein are used. They are used along with analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs). SYSADOAs are significant medications for pharmacological therapy of OA that help alleviate

and regulate symptoms, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis reports that (ESCEO) [21]. DCN begins to work within 4-6 weeks and continues to work for 4-8 weeks after the medicine is stopped [19, 20].

Role of IL-1B in the pathophysiology of type 2diabetes and beneficial roles dcn in type 2diabetes

Inflammatory pathways play an important role in the aetiology of type 2 diabetes and its long-term consequences, which is now widely acknowledged [22]. Both defective pancreatic β cell insulin secretion & insulin resistance in peripheral tissues are the two main pathophysiological mechanisms underlying type 2 diabetes development and progression, have immunoinflammatory-mediated bases, particularly those involving the proinflammatory cytokine interleukin-1β (IL-1β) pathways [23]. Various studies shows that Type 2 diabetes β cells exhibit higher amounts of IL-1β than non-diabetic controls [24]. Interleukin-1β (IL-1β) & tumour necrosis factor-α (TNF- α) have been implicated in pancreatic beta-cell apoptosis, resulting in decreased insulin production and the hyperglycemia associated with Type 2Diabetes [25,26]. (Fig 1). In overweight and obese people, disruption of inflammation of adipose tissue and endocrine function also causes systemic inflammatory responses and insulin resistance, which can contribute to development of Type 2Diabetes [27].

DCN's anti-inflammatory properties are attributed to a decrease in some cytokine concentrations, primarily IL-1β and TNF- α, which may contribute to the alleviation of insulin resistance [28]. DCN downregulate the expression and signalling of IL-1β, TNF-α & IL-6, and in the liver, adipose tissue, pancreatic islets, and muscle in animal models of obesity and diabetes [28,29]; and to increase βcell mass and insulin secretion by protecting βcells from apoptosis [30,31]. (Fig 2). DCN also improves glucose tolerance and lowers fasting glycemia levels by reducing peripheral insulin resistance, particularly in the liver and adipose tissue [29]. Furthermore, rhein has been reported to have therapeutic effects in diabetic nephropathy [32,33] and non-alcoholic fatty liver disease (NAFLD) caused by diabetes [34,35]. Apart from this effect, DCN also reduces the mean HbA1c level [36]. Peak effects can be observed after 24 weeks of DCN therapy.

Role of IL-1B in the pathophysiology of psoriasis and beneficial roles dcn in psoriasis

Psoriasis is defined by an autoimmune disorder in which skin cells multiplication occurs at 10 times than normal cells lead to formation of bumpy red patches covered by white scales. They can form on any body parts, although the majority of them appear on the scalp, knees, elbows and lower back. Psoriasis was once thought to be primarily a cutaneous disorder, but new research, including a metanalysis, has revealed that people with moderate-to-severe psoriasis had a higher cardiovascular risk, with more recurrent atherosclerotic events (such as myocardial infarction) [51].

The global incidence is estimated to be around 2%, however it varies by area.[43] Asian and some African ethnicities have a lower incidence, while Caucasian and Scandinavian populations have up to 11% [38,39,40].
Psoriasis vulgaris (Plaque psoriasis), Inverse psoriasis, Guttate psoriasis, pustular psoriasis, erythrodermic psoriasis are the most prevalent types of psoriasis among which 90% cases are Psoriasis vulgaris [41].

Sustained inflammation is a characteristic of psoriasis, which leads to uncontrolled keratinocyte growth and defective differentiation. Histology of the psoriatic plaque shows that epidermal hyperplasia (acanthosis) overlies inflammatory infiltrates of dermal dendritic cells, macrophages, T lymphocytes, and neutrophils [42]. Abnormal Tcell regulation along with interaction between complex cytokine network and keratinocyte plays important role in the pathogenesis & progression of psoriasis [43,44]. Any physical or chemical injury to the dysfunctional keratinocytes could stimulate cytokine synthesis and release, resulting in antigen-independent activation of T cells. This would then result in the production & release of more cytokines, keratinocyte growth, T lymphocyte proliferation, and inflammation. TNF-α, IFN-γ, IL-1(α &β), IL-2, IL-6 plays a povital role in the pathogenesis of psoriasis [45].

Both IL-1α and IL-1β are found in healthy epidermis [46,47]. Active IL-1β produced by proteolysis of precursor protein known as pro-IL-1β by the enzyme Caspase 1 (IL-1β converting enzyme or ICE). Cellular stress, infection and local inflammatory reaction activates Caspase 1 thus stimulates the production of IL-1β [46,48,49]. IL-1β shows autocrine & paracrine effects on keratinocytes, vascular endothelium, lymphocytes & local fibroblasts. Dermal endothelial cells produce ICAM and VCAM-1 in response to IL-1. Apart from these, platelet aggregating factor, nitric oxide, and PGI_2 secretions are also increased, all of which contribute to enhanced immune cell recruitment to the skin. Skin of psoriasis lesion and imiquimod (IMQ)-treated mouse shows increased expression of IL-1β. Furthermore, IL-1R signalling appears to be linked to the evolution of psoriasis and therapy response. IL-1 signalling is required for IMQ-induced skin inflammation in both dermal T cells and other cells like keratinocytes. In mice, IL-1β causes cutaneous proliferation of T cells and production of IL-17. Furthermore, IL-1 causes keratinocytes to release chemokines that predominantly chemoattract peripheral CD27 CCR6+IL-17 capable T cells (T17) [50]. Increased expression of IL-1β & IL-1α in psoriasis patient also contribute in vascular inflammation and atherosclerosis [52]. IL-1β shows pro-atherogenic effect by up-regulating multiple genes in endothelial cells, including CCL2, CCL5, and other genes. Chemokines like CCL2 and CCL5 encourage vascular inflammation by recruiting leukocytes to walls of the blood vessels. In normal circumstances, CCL2 expression is absent in endothelium, but its expression is raised in atherosclerosis and linked to an increased risk of myocardial infarction [53]. IL-1β up-regulated CD44 and vascular cell adhesion molecule-1 (VCAM1), which is consistent with another finding of IL-1 up-regulating VCAM1 in endothelial cells [54]. CD44 and VCAM1 both attract proinflammatory cells towards the vascular endothelium, and CD44 interacts with hyaluronan seen in high amounts in atherosclerotic lesions. Apart from these, IL-1β also promotes the expression of several genes in keratinocytes like CSF3 (Granulocyte colony stimulating factor), endothelin that participates in the process of atherosclerosis [55]. (Fig 1).

DCN inhibits the biosynthesis of IL-1β and shows antiatherogenic effect by inhibiting the IL-1β mediated activation of CCL2, CCL5 genes [55]. Apart from this, DCN also inhibits IL-1β mediated increased expression of CSF3 (Granulocyte colony stimulating factor), endothelin that also contribute its antiatherogenic effect. (Fig 2). DCN also inhibits IL-1α mediated IL-17C cytokine release from Th17 cells. IL-17C plays crucial role in the inflammatory reaction in psoriasis [56] and also participates in the inflammatory reactions of atherosclerosis [57]. In extracellular cells and keratinocytes diacerein counteracts IL-1β's pro-atherogenic and pro-inflammatory gene regulation, potentially limiting the advancement of skin inflammation and inflammation-induced atherosclerosis.

Role of IL-1B in the pathophysiology of epidermolysis bullosa and beneficial roles dcn in epidermolysis bullosa

Epidermolysis bullosa (EB) is a group of rare hereditary illnesses characterised by brittle skin blisters. EB most typically manifests in infancy and early childhood; however, it can also manifest later in puberty. Blisters on the skin can appear spontaneously or as a consequence of contact against the skin, slight damage, or even heat. EB patients are frequently referred as "Butterfly Children" because their skin is as fragile as a butterfly's wings.

Mutations in the keratin 14 (K14) or keratin 5 (K5) genes, which encode the primary intermediary filament components (IF) network in basal keratinocytes, produce inherited epidermolysis bullosa simplex type Dowling-Meara (EBS-DM). Heterodimers of K5 and K14 polymerize in healthy keratinocytes to form a cytoplasmic network that extends to the cellular periphery and provides stability to the stratified epithelia's basal layer. Causative mutations in EBS-DM cause the IF network to disintegrate and collapse, resulting in electron-dense clumps near the cytoplasmic periphery of keratinocytes [58]. EBS-DM cells are more susceptible to mechanical stress, heat, and osmotic shock, causes Dowling-Meara the most serious EBS subtype. As a result, even moderate damage causes blistering and tearing of mucous membranes and skins in EBS-DM patients [59]. IL-1β signalling is upregulated in EBS-DM keratinocytes, leading in JNK stress pathway activation and overexpression of K14 and IL-1 itself in a positive feedback mechanism. Expression of the predominately interfering mutant K14 allele also would rise as a consequence of this process, potentially exacerbating the EBS-DM pathology [60]. (Fig 1).

It would seem desirable to use a neutralising antibody or DCN to stop this positive feedback loop by suppressing IL-1β. Treatment of patient keratinocytes with these drugs not only reduced K14 and IL-1β expression and JNK phosphorylation, but also stabilised the IF network in response to heat shock. (Fig 2).

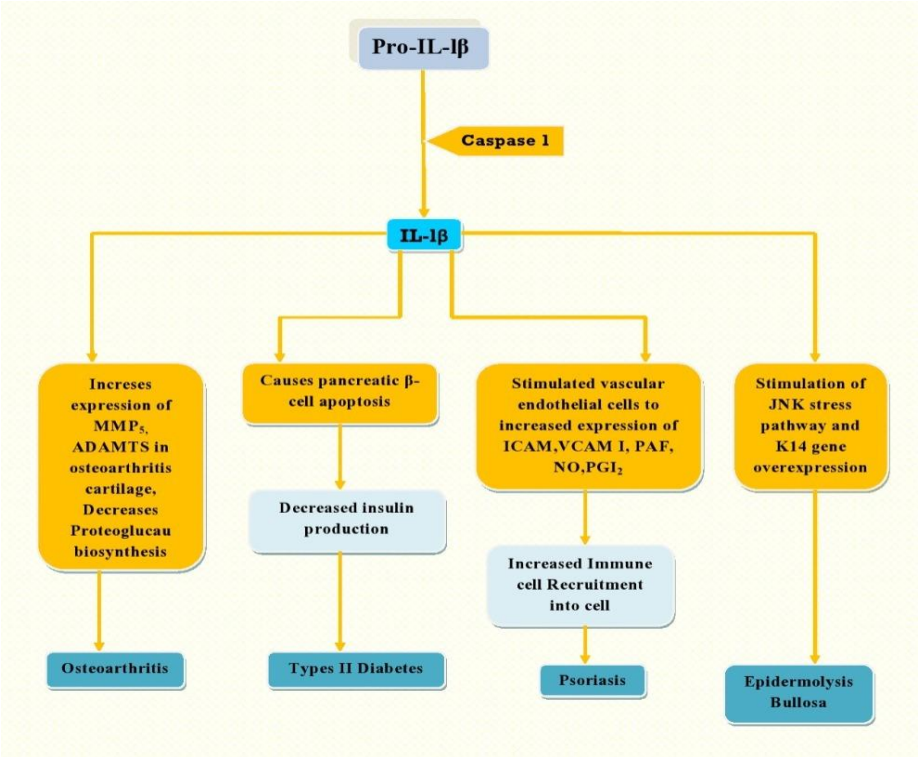


Fig 1: Role of IL-1β in pathogenesis of osteoarthritis, type II diabetes, psoriasis & epidermolysis bullosa

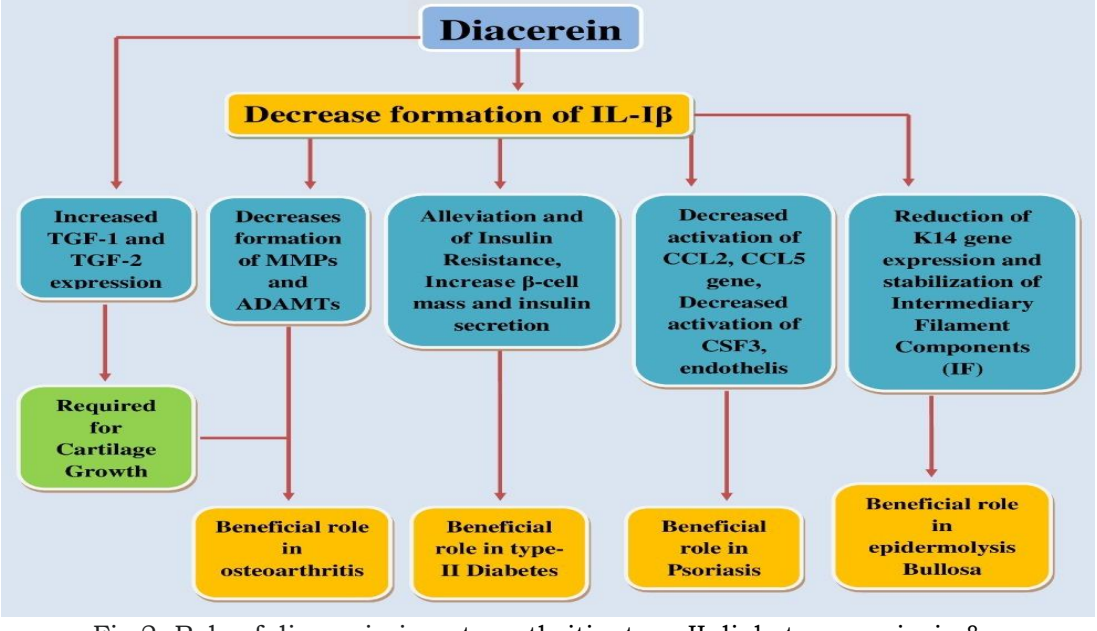


Fig 2: Role of diacerein in osteoarthritis, type II diabetes, psoriasis & epidermolysis bullosa

Conclusion

IL-1β plays a dominant role in the inflammatory reactions of osteoarthritis, epidermolysis bullosa, psoriasis and type II diabetes. It triggers the release of various proinflammatory cytokines and increases the expression of various cell adhesion molecules like ICAM and VCAM-1 that responsible for migration of leukocytes at the inflammatory sites. DCN having IL-1β biosynthesis inhibitory effect thus it reduces the expression of various proinflammatory reactions induced by IL-1β and can be considered as useful medication in the treatment of various IL-1β mediated inflammatory disorders.

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