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Review

Diacerein: Recent insight into pharmacological activities and molecular pathways

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ABSTRACT

Diacerein is a symptomatic slow-acting drug in osteoarthritis (SYSADOA) and the active metabolite is rhein. It is a non-steroidal anti-inflammatory drug with unique pharmacological properties as anti-oxidant and anti-apoptosis. Diacerein has recently shown to have a potential role by mediating anti-inflammatory as well as anti-oxidant and anti-apoptosis in kidney injury, diabetes mullites, and a beneficial effect on pain relief. It may have a therapeutic role in cancer, ulcerative colitis, testicular injury and cervical hyperkeratosis. Furthermore, diacerein has a valuable addition in combination therapy as a synergetic agent. This review, the first of its kind, highlights the proposed roles of diacerein in osteoarthritis and discusses recent results supporting its emerging roles with a particular focus on how these new insights may facilitate the rational development of diacerein for targeted therapies in the future.

1. Introduction

Diacerein is an anthraquinone derivative (Fig. 1b) [20], a non-steroidal anti-inflammatory drug, which has demonstrated great efficacy with safety profile and symptomatic slow-acting treatment of osteoarthritis. Clinically, diacerein has unique pharmacological actions and biological activities including anti-inflammatory, anti-catabolic, pro-anabolic properties on cartilage and synovial membrane. It also has protective effects against subchondral bone remodeling [1]. Recent studies have been shown that diacerein has protective effects against subchondral bone remodeling and the recommended starting dose is 50 mg once daily with evening meal for the first 2–4 weeks of treatment [2].

The principal mechanism of action of diacerein is to inhibit the interleukin-1b system and related downstream signaling [1]. In chondrocyte and synovial membrane of osteoarthritis, metalloprotease-3, collagenase, disintegrin, metalloproteinase domain with thrombospondin motifs-4.5, nitric oxide, inducible nitric oxide synthase, IL-1b-

Abbreviations: SYSADOA, symptomatic slow-acting drug in osteoarthritis; COX-2, cyclooxygenase-2; DKK, dickkopf; IL-1β, interleukin1β or Interleukin-1b; iNOS, inducible nitric oxide synthase; MMP, metalloproteinase; NO, nitric oxide; PGE2, prostaglandin E2; uPA, urokinase-type plasminogen activator; MAPK, mitogen-activated protein kinase; MEK/ER, mitogen-activated protein kinase/extracellular signal-regulated kinase; FAK, focal adhesion kinase; AP-1, activating protein-1; GLP-1, glucagon like peptide 1; DPP-4, dipeptidyl-peptidase 4; ER, endoplasmic reticulum; mRNA, messenger RNA; IL-6, interleukin 6; PRAC, pharmacovigilance risk assessment committee; EMA, European Medicines Agency's; TNF-α, tumor necrosis factor α; pIR-βp, Phosphorylated insulin receptor type β; pAkt, activated protein kinase B; STAT-3, signal transducers and transcriptional activators; AKI, acute kidney injury; PTP1B, protein-tyrosine phosphatase 1B; IRS-1, insulin receptor substrate1; MDA, malondialdehyde; HO-1, heme oxygenase −1; Nrf2, Factor-E2-related factor; ROS, reactive oxygen species; AQPs, aquaporins; NF-κB, nuclear factor kappa B; T2DM, type 2 diabetes mellitus; NAAA, N-acylethanolamine-hydrolyzing acid amidase; PEA, palmitoylethanolamide; AEA, N-arachidonoylethanolamide, also known as Anandamide; CXCL-13, C-X-C motif chemokine 13; TG, trigeminal ganglion; DRG, dorsal root ganglion; IBD, inflammatory bowel disease; UC, ulcerative colitis; NSAIDs, non-steroid anti-inflammatory drugs; CdCl2, cadmium; NLRP3, NOD-like receptor family protein 3; TIR, testicular injury; DN, diacerein; SST, somatostatin analogue; NSCLC, non-small cell lung cancer; MTX, methotrexate; NAFLD, non-alcoholic fatty liver patients; EBS, epidermolysis bullosa

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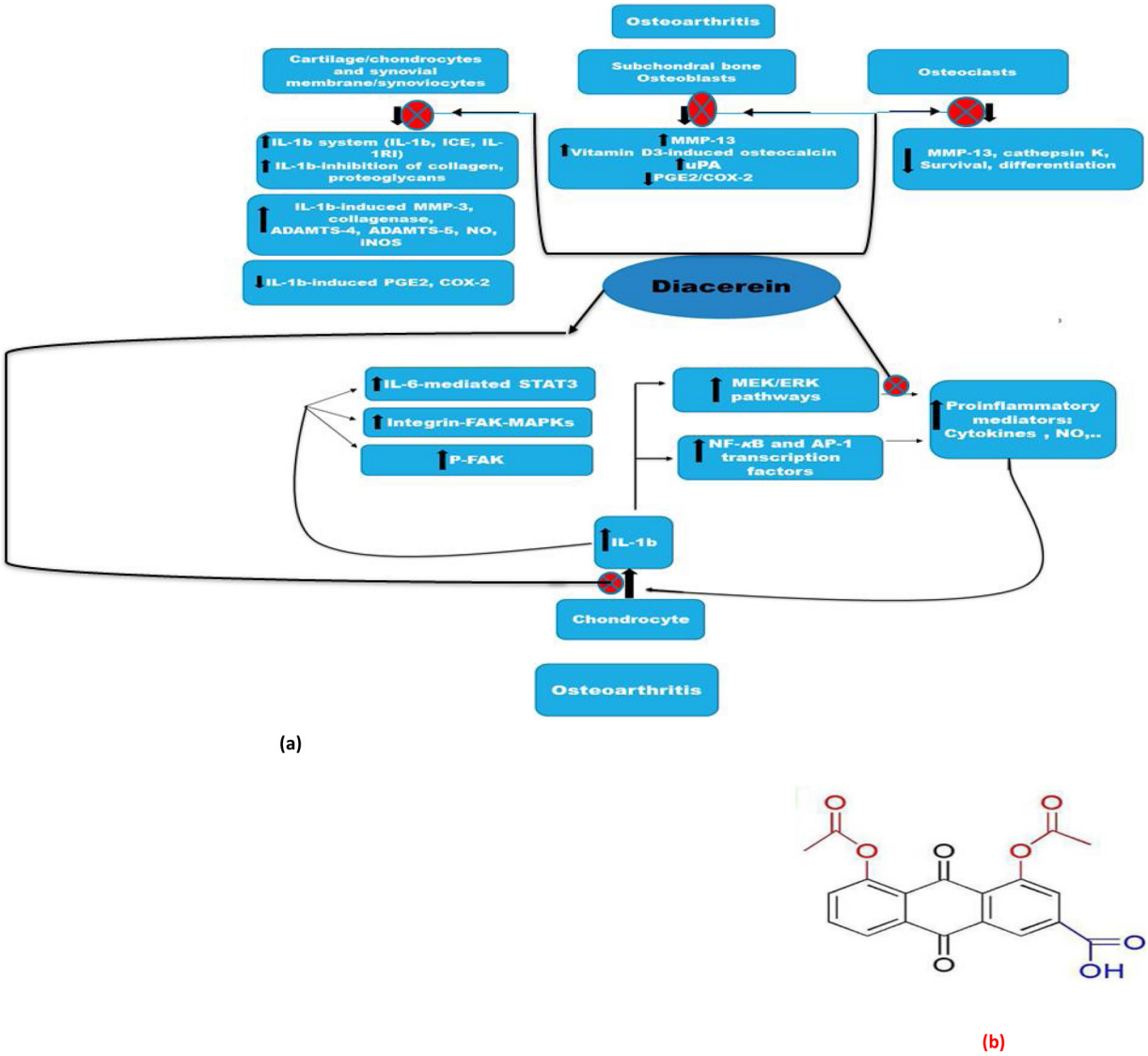

Fig. 1. (a) Summary of the influence of diacerein on osteoarthritis. **(b)** the chemical structure of diacerein.
ADAMTS: disintegrin and metalloproteinase domain with thrombospondin motifs; COX-2: cyclooxygenase-2; DKK: Dickkopf; IL-1b: interleukin-1b; iNOS: inducible nitric oxide synthase; MMP: metalloproteinase; NO: nitric oxide; PGE2: prostaglandin E2; uPA: urokinase-type plasminogen activator; MAPK: mitogen-activated protein kinase; MEK/ER: mitogen-activated protein kinase/extracellular-signal-regulated kinase; FAK: focal adhesion kinase; AP-1: activating protein-1.

inhibition of collagen, and proteoglycans downregulated whereas, IL-1b-induced prostaglandin E2 and cyclooxygenase-2 upregulated in diacerein treatment. On the other hand, diacerein modulated metalloprotease-13, vitamin D3-induced osteocalcin, urokinase-type plasminogen activator, prostaglandin E2 and cyclooxygenase-2 in subchondral bone osteoblasts as well as metalloprotease-13, cathepsin K with cell Survival and differentiation decreased in osteoclast [3]. Following the interaction between IL-1 and cell surface receptors, there is an activation of the mitogen-activated protein kinase (MAPK) pathway through the inhibition of the MEK/ERK (mitogen-activated protein kinase/extracellular-signal-regulated kinase) cascade. [4]. Moreover, diacerein modulates integrin-FAK-MAPKs, STAT3 and focal adhesion kinase (FAK) in osteoarthritis chondrocytes and reduces IL-6 by blocking the IL-1β pathway via MEK/ERK and NF-κB DNA binding [5]. (Fig. 1a) summarized the role of diacerein in osteoarthritis. Diacerein has few adverse side effects, the most common adverse side effects being common gastrointestinal disorders, mostly soft stools, and diarrhea. In 2014, the Pharmacovigilance Risk Assessment Committee (PRAC) and the European Medicines Agency's (EMA) committee established the safety profile of diacerein, which has not changed in the last two decades, and decided that its benefit-risk balance remained positive in the symptomatic treatment of knee and hip OA [1]. Since diacerein's worldwide spread for over 20 years, numerous studies concerning other potential indications have illustrated many promising pharmacological effects (Summarized in Table 1) includes nephrotoxicity and kidney injury protective effect [6,7], glycemic control [8,9], improvement in insulin sensitivity and glucose tolerance [10], the antinociceptive effect [11–13], anti-neuropathic pain [14], anti-inflammatory pain [15], anti-ulcerative colitis [16], testicular injury protective effect [17,18], cervical hyperkeratosis preventive effect [19], the anti-cancer effect [20–22], the hepatoprotective effect [23–25], a therapeutic role in epidermolysis bullosa [26], thyroid dysfunction [27] and management of the periodontal disease [28,29] as well intervertebral disc degeneration [30]. In addition to cardiac function improvement effect [31], it has a valuable addition in combination therapy as synergetic agent [13,20,32–34]. In this article, we review the recent findings related to diacerein and summarize the mechanism of action of diacerein that may provide a framework of specific targeted therapies.

Table 1
Summary of the biological activities of diacerein/Rhein.

Model	Doses	Drug activity	Effects	Reference
Rats	Diacerein 25 and 50 mg/kg/day	Anti-oxidant,anti-inflammatory, anti-apoptotic and anti-necroptotic effects	Protects against glycerol-induced AKI	[6]
Rats	Diacerein 30 mg/kg/day	Anti-inflammatory and anti-oxidant	Alleviates kidney injury	[7]
Mice	Diacerein 5, 10 and 50 mg/kg/day	Anti-inflammatory	Decreases the autoimmune diabetes frequency	[54]
Mice	Diacerein 20 mg/kg	Anti-inflammatory	Improves glucose tolerance and insulin Sensitivity	[53]
Human	Diacerein 50 mg once daily	Anti-inflammatory	Insulin secretion increased and metabolic control improved	[50,55]
Human	Diacerein 50 mg once daily	Anti-inflammatory	Improves glycemic metabolic control	[50]
Rats	Diacerein 100 mg/kg/day	Anti-inflammatory	Reduces insulin resistance	[8]
Mice	Diacerein 25 mg/kg, 50 mg/kg & 5.0–25.0 mg/kg	Anti-inflammatory and inhibition of glutamatergic, neurotransmission	Decreases visceral pain (antinociception)	[12]
Rats and human	Diacerein 10 mg/kg, 19 mg/kg & 25 mg/kg	Anti-inflammatory and inhibition of palmitoylethanolamide inactivation	Anti-inflammatory pain effect	[15]
Rats	Diacerein 50 mg/kg/day	Anti-oxidant, anti-inflammatory, anti-apoptotic	Beneficial effects against ulcerative colitis	[16]
Rats	Diacerein 50 mg/kg/day	Anti-inflammatory and anti-oxidant	Protective effect against testicular injury	[17,18]
Rats	Diacerein 50 mg/kg/day	Anti-oxidant, anti-inflammatory, anti-apoptotic	Treatment effect in female endometrial hyperplasia and cervical hyperkeratosis	[19,84]
Rats	Diacerein 20 and 40 mg/kg	Anti-inflammatory and induce apoptosis in breast cancer cells	Therapeutic effect in breast cancer	[20,21]
Mice and human	Rhein (60 and 100 mg/kg) Rhein and diacerein (30, 60, 100 μM)	Anti-inflammatory, and stimulate apoptosis in human NSCLC cells	Potent efficacy against non-small-cell lung cancer	[22]
Human	Diacerein 100 mg/day	Anti-inflammatory	Reducing liver steatosis and fibrosis	[83]
Mice	Rhein 150 mg/kg in water daily	Anti-inflammatory	Ameliorates fatty liver disease	[25]
Rats	Rhein 50 and 100 mg/kg	Anti-inflammatory	Hepatoprotective ability in patients receiving MTX treatment	[23]
Rat	Diacerein 30 mg/kg/day	Anti-inflammatory and anti-peroxidative	Thyroid function improvement	[27]
Rats	Diacerein 100 mg/kg/day	Anti-inflammatory	Managing of periodontal disease	[28,29]
Rats	Diacerein 80 mg/kg	Anti-inflammatory	Improves left ventricular remodeling and cardiac function	[31]

2. Kidney and diacerein effect

Acute kidney injury (AKI) is a crucial clinical disorder with a huge health problem over the world. Thus, the efforts for valuable therapy to accelerate the cure and/or to avoid AKI has attracted much attention [35]. The protective effect of diacerein in the kidney has been demonstrated in different models of nephropathy as IgA induced nephropathy, obstructive nephropathy, chronic allograft nephropathy, and high glucose and angiotensin II-induced nephropathy [36].

Many studies have been conducted to confirm the protective role of diacerein and its active metabolite rhein in AKI. Al-Saedi et al. and Rashid et al. observed that the histopathological changes significantly improved with coadministration of diacerein in doxorubicin-induced nephrotoxicity treated group (25 and 50 mg/kg/day) [37,38]. As well as, Zhao et al. reported the antioxidant protective effect of rhein on acetaminophen-induced hepatotoxicity and nephrotoxicity in rats. Downregulation of malondialdehyde (MDA) and total nitrites (NOx) on coadministration of rhein plus acetaminophen group compared to the acetaminophen group was observed [36]. A recent study of AKI induced by glycerol, and nephrotoxicity showed that functional and structural changes in kidney were significantly attenuated by modulating inflammation, oxidative stress, apoptosis and necroptosis with diacerein (25 and 50 mg/kg/day) [6,35].

Related studies have examined the protective effect of rhein lysinate (RHL) (25 and 50 mg/kg/day) against kidney impairment in senescence-prone inbred strain 10 (SAMP10) mice. MDA levels significantly decreased in the kidney after treatment with RHL [39]. Moreover, diacerein treatment also associated with diminished the rise in heme oxygenase −1 activity (HO-1) in glycerol-induced AKI and that the effect was dose-dependent (25 and 50 mg/kg/day) [6]. The results came in line with Chueakula et al., who attributed the decreasing of HO-1 level in the diacerein-treated group to reduced nuclear factor-E2-related factor (Nrf2) expression and hence inactivation of Nrf2 pathway and Nrf2-mediated antioxidant enzymes as HO-1 [7]. Additionally, there is an increasing trend for an accumulation of evidence as a potential antioxidant effect of diacerein [6,37,38]. Boutaud et al. suggested that renal oxidative markers might be accredited to myoglobin deposition that generates mitochondrial reactive oxygen species (ROS) production, recruits lipid peroxidation along with antioxidant enzymes depletion. [40]

Interestingly, the levels of free radical scavengers have been reported to be reversed in a dose-dependent manner by diacerein treatment (25 and 50 mg/kg/day) which indicated to suppression ROS production and its potent antioxidant capacity [6,41]. Besides antioxidant properties, the anti-inflammatory activity of diacerein on diabetic nephropathy had also been proved and may be effective in the pathogenesis of diabetic nephropathy through suppressing the inflammatory cytokines [12,42]. In addition to decreases level of inflammatory mediators, a study on endotoxin-induced AKI detected that rhein (diacerein-derived metabolite) significantly improves the renal function, decrease the concentration of serum urea and creatinine along with strongly attenuate the severity of renal injury in vivo and in vitro experimental sepsis [43].

To improve renal function, in parallel with the reduced inflammation, it was reported that diacerein (50 mg/kg/day) attenuated not only renal inflammation, decreased renal inflammatory cytokine secretion but also altered tubular water and sodium handing, blocked the reduction of aquaporins AQPs (AQP1, AQP2, AQP3) and sodium transporter expression leading to an improvement of renal function [44].

These findings may agree with Zhou et al. and Mehta et al. who reported that the diacerein has also been shown to improve renal function, in parallel with the reduced inflammation, in diabetic nephropathy in mice as well as doxorubicin nephrotoxicity in obese insulin-resistant rats and ameliorated renal injury in several animal models [45,46].

The renoprotective effect [47] and renal function improvement

activity in nephropathy animal models was demonstrated as a result of attenuating inflammation and oxidative stress [7]. Diacerein intake was also associated with the anti-apoptotic effect [48]. This effect reported by Z.Q et al. in the early phase of glomerulosclerosis. Rhein (150 mg/kg/day) was protected against kidney injury by decreasing the activities of caspase-3 and nuclear factor kappa B (NF-κB) as well as ameliorated renal lesions [49]. Overall, diacerein (25 and 50 mg/kg/day) has been reported for its potential applications in the improvement of AKI via inflammatory pathway modulation, anti-oxidant, anti-apoptotic and anti-necroptotic effects [6]. Concluding that, the many pharmacological activities, including anti-inflammatory, antitumor, and antioxidant of rhein (75, 150, and 300 mg/kg) have been previously described. It also significantly improves the symptoms of nephropathy via decreasing proinflammatory cytokines production, including IL-1β, TNFα and prostaglandin E2. [48].

3. Diabetes disease and diacerein effects

Many clinical studies have shown that diacerein has beneficial effects and reduces the incidence of diabetes disease [8,9,50]. In Mexico, a randomized clinical trial in drug-naïve patients with type 2 diabetes mellitus (T2DM). The insulin secretion increased and glycemic metabolic control improved with diacerein administration (50 mg once daily) [50]. A small clinical trial found that the oral dose of diacerein (50 mg/day) for 90 days as an add-on to metformin in patients with T2DM showed an improvement in glycemic control compared with the placebo group [9]. Moreover, a random clinical trial assessed the efficacy and safety of a 48-week treatment with diacerein (100 mg/day) in patients with T2DM. The diacerein was well tolerated and useful as an assistant treatment in patients with type 2 diabetes. The peak of improvement in glycemic control (HbA_{1c}) was at the 24th week of treatment compared with placebo ($P = 0.014$) and ($P = 0.005$), respectively [8]. Furthermore, the efficacy of the drug on obesity and diabetes in animal models was recorded that diacerein (50 mg/kg/day) has been demonstrated to increase insulin secretion and beta-cell mass [51,52] and reduce peripheral insulin resistance, particularly in the liver and adipose tissue [53] resulting in a marked improvement in glucose tolerance [51,54].

In addition to the capacity of diacerein in increasing insulin secretion [51–53], improvement in glycemic metabolic control [8,9] glucose tolerance enhancement [51–54], decreasing the diabetes frequency [54], lowering of fasting glucose [9,50,53], reducing postprandial glucose [9] and HbA1c [8,9,50]. It is claimed that diacerein intake was also associated with a decrease of diabetes frequency with down-regulating proinflammatory cytokines, such as IL-1β and TNF-α [50,53,54]. A related study reported that the decrease of inflammatory cytokines by diacerein did not accompany changes in insulin sensitivity after diacerein administration in a clinical trial was carried out in 40 adult patients with type 2 diabetes. Although, there is a significant decrease in fasting glucose ($P < 0.01$) and in HbA_{IC} levels ($P < 0.001$) in diabetic patient after diacerein administration with significant elevate in first ($P < 0.01$), late ($P < 0.01$), and total insulin, ($P < 0.01$) secretions and significantly decreased TNF-a and lL-lß [50].

Similarly, diacerein treatment was associated with a decrease of the diabetes frequency, HbA_{IC} levels and proinflammatory cytokines TNF-a and IL-1-β according to Malaguti et al. [54], Tobar et al. [53] and Tres et al. reports [55]. Inhibition of IL-lß and TNF-a has been suggested as a possible mechanism way through which diacerein administration may have potential usefulness in the treatment of T2DM [50,53] which resulted in an improvement in glucose tolerance and in insulin signaling mainly in the adipose tissue and liver [50]. Therefore, this medicine (20 mg/kg/day) may be an alternative therapy for insulin resistance with enhancement insulin sensitivity in obesity, mediated by the reversal of subclinical chronic inflammation [53]. Moreover, Pakala et al. and Pelletier et al. supported the association between the anti-inflammatory effect for diacerein and diabetes. They reported that the most suitable property attributed to diacerein is the inhibition of proinflammatory cytokines, such as IL-1β and TNF-α synthesis [56,57] leading to improves insulin sensitivity and regulation of insulin signaling [58].

A study on targeting inflammation in the treatment of T2DM showed that the fundamental role of inflammatory pathways in T2DM pathogenesis and its associated long-term complications is well accepted [59]. The two main physiopathological mechanisms underlying T2DM development and progression, namely defective pancreatic b-cell insulin secretion and peripheral insulin resistance, both have inflammatory-mediated bases and closely related to interleukin-IL-1b pathways [59,60]. Suggestions that were targeting inflammatory pathways may be a potential treatment for T2DM [61,62].

Interleukin IL-1β and tumor necrosis factor-α TNF-α have been involved in apoptosis of pancreatic beta-cells, decreasing insulin secretion with the consequential hyperglycemia characteristic of T2DM [61,63]. Besides, dysregulation of inflammation of adipose tissue and endocrine function also induces systemic inflammatory pathways and insulin resistance in overweight patients and obesity, which may lead to T2DM development [64]. Therefore, the anti-inflammatory capacity of diacerein due to the decrease of some cytokine concentrations, mainly IL-1β and TNF-α, that may be responsible for the improvement of insulin resistance [54] and the diacerein could be considered as a pharmacological option to counter the systemic inflammation and insulin resistance characteristic of patients with obesity due to anti-inflammatory effects [9].

While the related study on T2DM patients did not support the anti-inflammatory effect of diacerein. There are no significant effects of diacerein observed regarding serum inflammatory biomarkers, and lack of any effect on fasting glycemia levels. Although compared with placebo, significantly reducing mean HbA1c was showed by 0.41 % ($P = 0.023$) in the per-protocol analysis and by 0.35 % ($P = 0.038$) in the intention-to-treat (ITT) analysis. The authors proposed, although significantly reducing mean HbA1c, that the result of the lack of any effect of diacerein on level of fasting glycemia was intriguing [8].

The suspected mechanism of diacerein in glycemic control compared with metformin (is an oral glucose-lowering agent) has been previously described by Villa et al. [9] and summarized in (Fig. 2).

4. Pain and diacerein effects

Pain can be broadly divided into three classes: nociceptive pain, pathological pain and neuropathic pain [65]. At the daily oral dose of 50 mg/kg, diacerein is known to produce efficacious anti-inflammatory and analgesic actions, and even a slight disease-modifying action, in patients with osteoarthritis [66], and demonstrated benefits in alleviating joint pain in humans and in rodent models of the disease in vivo and in vitro [12]. Its effect on different types of pains had been studied extensively, which confirmed the significant role of diacerein in pain relief [11,12,14,15].

Diacerein has been reported for its substantial potential effect against three types of pain, the antinociceptive effect [11–13], anti-neuropathic pain [14], anti-inflammatory pain [15]. Practically, in a rat model of acute inflammatory pain, analgesic activity for diacerein with a potent and selective inhibitor of palmitoylethanolamide inactivation was reported [15]. Based on experimental results, Bisogno et al. and Di Marzo et al. found that the mammalian cells produced palmitoylethanolamide (PEA) [67,68] during neurodegenerative conditions and inflammatory to exert analgesic and anti-inflammatory properties [69]. PEA inactivated to ethanolamine and palmitic acid, more specifically, by N-acylethanolamine-hydrolyzing acid amidase (NAAA) [70]. PEA can produce the anti-nociceptive and anti-inflammatory effects performed by another fatty acid anandamide (AEA), ethanolamide which is often synthesized together with PEA [68,71,72]. Experimental studies of pain have also revealed the antinociception effect of diacerein [11–13]. In vitro and in vivo experimental models, diacerein (10, 25 mg/kg) exhibited a high inhibitory activity on human recombinant

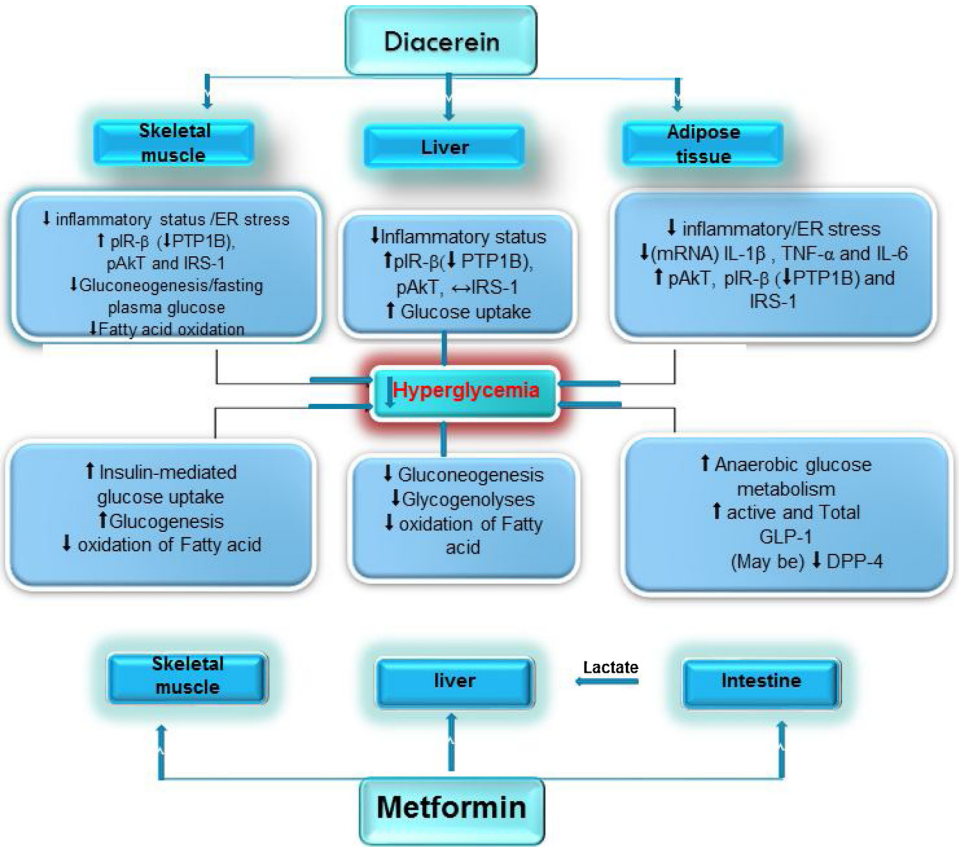

Fig. 2. Mechanism of action of diacerein and metformin for glycemic improvement.
GLP-1: glucagon like peptide 1; DPP-4: dipeptidyl-peptidase 4; ER: endoplasmic reticulum; mRNA: messenger RNA; IL-6: interleukin 6; IL-1β: interleukin1β; TNF-α: tumor necrosis factor α; pIR-β: phosphorylated insulin receptor type β; PTP1B: protein-tyrosine phosphatase 1B; IRS-1: insulin receptor substrate1; pAkt: activated protein kinase B.

NAAA and significantly inhibited inflammation which led to increasing endogenous levels of PEA. NAAA inhibition might be the mechanism through which this compound exerts its effects, as well as a suitable therapeutic strategy to reduce inflammatory pain also in humans [15].

A study on visceral and somatic pain reported that the antinociceptive effect performed by diacerein might be depending on a direct effect on pro-inflammatory cytokines released after glutamate agonist injection. Diacerein (25 mg/kg, intraperitoneal injection.) showed to inhibit significantly and dose-dependent the nociceptive responses induced by IL-1β and TNF-α as well as inhibiting glutamatergic transmission. [12].

Furthermore, inhibition of neuropathic pain by diacerein was examined and presented that neuropathic pain induced by partial ligation of the sciatic nerve was inhibited with diacerein treatment (25, 50, and 100 mg/kg) and produced anti-allodynic effects against carrageenan- and complete Freund's adjuvant (CFA)-induced inflammatory nociception [73].

C-X-C motif chemokine 13 (CXCL13) has been documented to mediate orofacial neuropathic pain in the trigeminal ganglion (TG) of mice. Moreover, a study revealed the critical role of diacerein (5 μg intra-TG injection) in blocking CXCL13 and reducing neuropathic pain via proinflammatory cytokines TNF-α and IL-1β downregulation [14]. These results supported by Watkins et al., who found that neuropathic pain was inhibited by decreasing the level of proinflammatory cytokines as TNFα and NFκβ. In addition, it was confirmed that TNF-α and IL-1β are important proinflammatory cytokines that mediate chronic pain in both dorsal root ganglion (DRG) and spinal cord [74], essential in mediating orofacial neuropathic pain [14] as well as regulating chronic pain in both the peripheral nervous system and the central nervous system [75].

On the other hand, according to Raffa, that the combination treatment is commonly used to improve pain management and minimize the incidence of adverse side effects, while the analgesic effects can be maximized [76]. The combination therapy of diacerein (10–300 μg/paw and 12.50–200 mg/kg), and antiepileptic (gabapentin, topiramate, and carbamazepine) in the rat formalin test, showed the efficacy of combination therapy better than monotherapy in pain management. The diacerein has been found to possess a significant and dose-dependent antinociceptive role for its use as an antinociceptive effect through a synergistic combinational approach with an antiepileptic drug. Concluding that the reduction of almost half of the dose requirements with a safe adverse effect profile proposes that these combinations may well have clinical importance to control inflammatory pain [13]. The summary of the role of diacerein in pain, shown in the (Fig. 3).

5. Gastrointestinal protective effect of diacerein

Inflammatory bowel disease (IBD) is a chronic inflammatory, life-threatening disease affecting the colon, including ulcerative colitis (UC) which is a premalignant disease. The drugs used in the treatment of UC, such as biologic medications, corticosteroids, aminosalicylates and immunosuppressants aim to reduce symptoms or to maintain remission, but they can have side effects as nephritis, fluid retention immunosuppression, hepatitis and others [77]. Ongoing investigations aim to explore new preparations that may be more beneficial in ameliorating the disease or have synergistic and additive effects to the previously used therapies for better disease control with less adverse effects [78].

A study in Egypt, on acetic acid-induced ulcerative colitis in rats, documented that diacerein (50 mg /kg) pretreatment performed significantly alleviating effect against the UC model. Suggested that probably attributed to its anti-oxidant anti-inflammatory and anti-apoptotic effects [16]. Besides activity against ulcerative colitis, it is reported that diacerein has an anti-gastric ulcer effect by inhibition of ROS production. Diacerein (10, 30, 100 mg/kg) significantly inhibited gastric ulceration induced by indomethacin and HCl/ethanol in a dose-

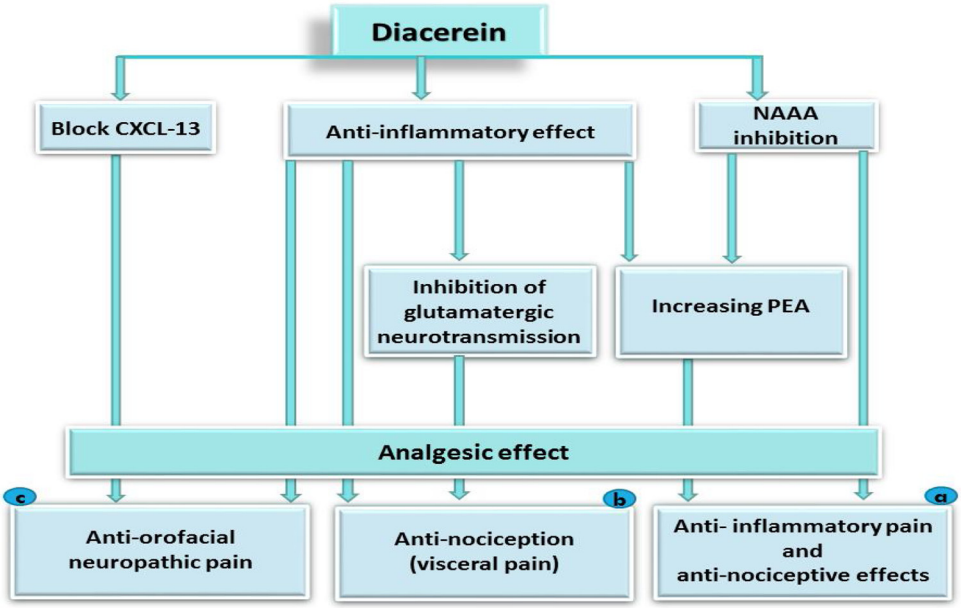

Fig. 3. Some ways by which the diacerein relieve pain.
a- Diacerein inhibited human recombinant NAAA and inflammation and followed by elevation of PEA levels which is able to enhance the anti-inflammatory and anti-nociceptive effects. b- Diacerein produced antinociception by inhibiting glutamatergic transmission as well as activity of pro-inflammatory cytokines. c- Diacerein inhibited orofacial neuropathic pain through partially blocking of CXCL13 and inhibition of proinflammatory cytokines.

dependent manner. The mode of action might be inhibiting ROS production. Summarizing that duo to diacerein prevents gastric ulceration induced by non-steroid anti-inflammatory drugs (NSAIDs), it might be beneficial in combination with NSAIDs in the treatment of chronic cases of joint diseases during clinical therapy [79].

6. Role of diacerein in testicular injury and cervical hyperkeratosis

In recent studies, an exciting role of pharmacological activities of diacerein including, anti-testicular injury effects and anti-cervical hyperkeratosis effect via anti-inflammatory, anti-oxidant and anti-apoptotic activity have been explored [17–19]. Diacerein (50 mg/kg/day) has been found to significantly protect the testicular toxicity induced by cadmium in the rat model. The changes in the biochemical markers observed with cadmium (CdCl2) injection were significantly alleviated with diacerein intake as well maintained the normal testicular architecture, preserved spermatogenesis, and reduced the expression of NOD-like receptor family protein 3 (NLRP3) inflammasome in testes [18]. Similarly, previous studies on male gonadal toxicity induced by cadmium revealed that anti-apoptotic agents and anti-inflammatory effectively guarded against testicular toxicity [80,81].

Da Silva et al. [82] and Leite et al. [83] showed that diacerein significantly guarded against apoptotic and inflammatory injuries in both human and animal research. The mechanisms of diacerein action include its ability to inhibit caspase-1 necessary for IL-1β activation and to downregulate IL-1β-specific receptors [4,17]. Furthermore, a recent study, ischemia-reperfusion-induced testicular injury (TIR) in rats, revealed that diacerein (50 mg/kg) has a strong protective effect against dysfunction and experimental testicular injury via its anti-inflammatory and antioxidant activities. Diacerein was also able to normalize both serum testosterone and testicular weight, with correction of histopathological changes along with a reduction of oxidative stress parameters and IL-1 b induced by TIR [17]. These results in accordance with a report by Yu et al. which found that the structural, functional and metabolic disturbances were ameliorated with diacerein treatment (50 mg daily), that is indicative to the protective effect against TIR which may be attributed to its anti-oxidant, anti-inflammatory and consequently anti-apoptotic effect which was previously documented [34].

On the other hand, female cervical hyperkeratosis was prevented with use diacerein (50 mg/kg/day) and improved all abnormal measured parameters to normal values via its anti-inflammatory, antioxidant and antiapoptotic effects [19].

7. Anti-cancer effect of diacerein

Emerging evidence suggests that diacerein has significant antitumor effects, supporting the potential uses of diacerein as an antitumor agent [84]. The role of inflammatory cytokines, especially IL-6, in the development and progression of many inflammatory conditions as well as cancer, was reported [85]. Increased level of IL-6 has been reported in a wide range of cancers, such as breast cancer [86]. It is reported that IL-6 participates in tumor progression by activating some tumorigenic pathways [87].

Many reports demonstrated that diacerein also has an important role in the inhibition of some types of cancer and able to fight against tumors via IL-6 modulation and that diacerein-prompted apoptosis was correlated with suppression of IL-6/STAT3 [20–22].

An experimental study, the role of diacerein (50 mg/kg/day) in endometrial hyperplasia and atypia, showed significant enhancement of the histopathological changes, repress tumor growth in endometrial hyperplasia by inhibition of proinflammatory cytokines pathways and increased apoptosis in tumor remnants [84].

The results support the previously suspected anticancer influence of diacerein as reported by Bharti et al., remarkably the potent apoptotic and antiproliferative effect of diacerein (20 and 40 mg/kg) was detected against breast cancer. The antitumor effect was correlated with hampering IL-6/IL-6R/STAT3/MAPK/Akt network cancer (Fig. 4) pathway and considered a novel blueprint for cancer therapy [21]. Additionally, it has been proven a valuable addition of diacerein in combination therapy for which the drug has shown synergistic actions. The drug became advantageous for a combinational therapeutic approach. In a study on breast cancer therapy, diacerein (DN) has been found to potentiate the effect of somatostatin analogue (SST) against breast cancer cells. Moreover, the combination displayed significantly better anti-tumor efficacy as compared to free drug in breast cancer models by inducing apoptosis in breast cancer cells and effectively inhibiting the oncogenic IL-6/ IL-6R /STAT3/MAPK/Akt signaling pathways. It is proposed that the combination provides a novel strategy with better efficacy for breast cancer therapy [20].

Furthermore, the effect of the drug on non-small cell lung cancer (NSCLC) have been evidenced. A recent study has focused on the specific molecular mechanism of action of rhein and diacerein (60 and 100 mg/kg; 30, 60 and 100 μM) that exert their antitumor effects against

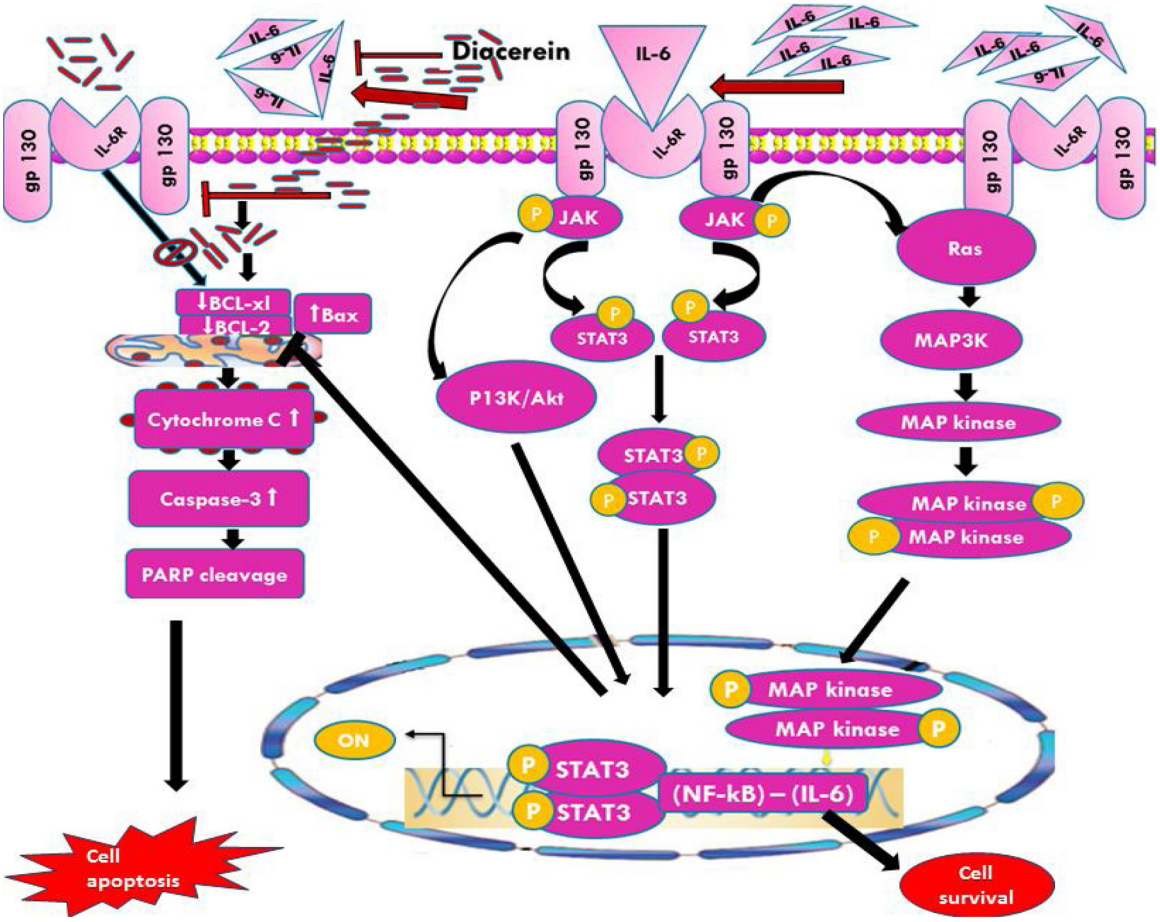

Fig. 4. The role of diacerein in breast cancer therapy.
IL-6/IL6R contributes to tumor progression through sequentially activating many tumorigenic pathways: JAK1/JAK2/STAT3, Ras/Raf (MAP3k)/MAPK (MAP kinase) and PI3K/Akt oncogenic signaling pathways. Activated STAT3 and MAPK participate in cell survival and tumor progression by regulating Bcl-2 family proteins and activate NF-kB which is the transcription factor that promotes the transcription of inflammatory cytokines e.g. IL-6. Expression of anti-apoptotic proteins Bcl-2 and Bcl-xL were reduced, as well as apoptotic protein Bax was upregulated in diacerein-treated breast cancer cells. Expression of IL-6/IL-6R and its related mediators P-STAT3, P-MAPK and Akt were also inhibited.

non-small-cell lung cancer. These findings indicated the potent effectiveness against non-small-cell lung cancer via inhibiting the IL-6/STAT3 pathway. Rhein has a promising potential to be applied as a novel antitumor therapy for NSCLC [22].

8. Hepatoprotective effect of Diacerein

In the 2018 study by Tianci et al., diacerein (50 and 100 mg/kg) has been found to protect the liver injury. The hepato-protective characteristic of the drug was due to its protective action against liver toxicity and liver damage induced by methotrexate (MTX). An extra feature of the drug (5, 10 and 20 μM) is its capacity to increasing the cell survival rate and reduced the number of apoptosis cells in MTX-treated normal human hepatocyte (L02 cells). Moreover, diacerein significantly reduced the elevation of liver enzymes and improved liver morphological damage induced by MTX [23].

Furthermore, in 2019, a randomized, placebo-controlled trial, 2-year diacerein (100 mg/day) use in non-alcoholic fatty liver patients (NAFLD) and T2DM disease. Liver stiffness was significantly decreased which reflects fibrosis diminution in contrast to placebo by 1.6 kPa (95 % CI: –2.6 to −0.5 kPa; $p = 0.003$). Eight patients diminished fibrosis stage through treatment, seven of whom were in the group of diacerein ($p = 0.020$) [83]. Besides, data from animal investigations showed that diacerein inhibits inflammatory cytokines and enhances insulin resistance in the adipose tissue and liver [53,54], resulting in useful influences in experimental NAFLD models [25,88]. Contrary, Zheng et al. reported that diacerein could cause a hepatic adverse events, but the extensive preclinical animal toxicology data with diacerein indicated that the liver was not a target organ for toxicity [89]. The mechanism of action of this hepatic toxicity is not fully understood, but an idiosyncratic mechanism is suggested [1].

9. Diacerein as synergetic agent

The additional vital aspect of diacerein is its use in combinational studies. Besides the single effect of the drug, it has also been discovered that the drug has a strong synergistic effect. Many studies have documented that diacerein plays a critical role and a combined therapeutic approach may be established more beneficial than signal therapeutic agent [13,32–34]. In a prospective clinical study, diacerein (50 mg daily for the first 2 weeks and twice per day for another 10 weeks) has been found to potentiate the effect of febuxostat drug against refractory gout. The treatment with both drugs for 12 weeks synergistically had a better therapeutic effect along with reducing the levels of serum IL-1b and serum amyloid with enhancement effect on joint damage and alleviating disease activity of refractory gout as compared with febuxostat [34].

In the research of Jia ZH et al., rhein was studied in combination with benazepril on the treatment of and explored the ability to induce renal-protection of combined therapy in diabetic nephropathy on

mouse of T2DM model. These findings suggest that a therapeutic approach combining rhein (150 mg/kg/day) and benazepril may be useful in the treatment of diabetic nephropathy compared with the therapeutic effects of single treatment [32].

In addition, the other combination was aimed to evaluate the treatment effect of celecoxib (CLX) combined with diacerein (knee joint injection of 0.045 mg/mL) on OA and delineate the underlying molecular mechanism. Compared with single treatments, the combination was markedly capable of attenuated OA, improved bone cartilage metabolism, and suppressed chondrocyte apoptosis with inhibition of inflammatory mediators by regulating three signaling pathways, including NF-κB, JNK and p38 MAPK Signaling Pathways. The conclusively resulted in therapeutic actions and suggested that combination has satisfactory treatment effects on OA [33].

On the other hand, in one study in which diacerein loaded liposomes (DNL) were prepared and decorated with somatostatin (SST-DNL). SST-DNL displayed significantly better anti-tumor efficacy as compared to free diacerein (DN) and DNL in breast cancer in rat models [20]. Furthermore, the diacerein has been found to have a significant effect as an antinociceptive agent by a synergistic combinational approach with an antiepileptic drug. The combination therapy of diacerein with each antiepileptic drug (gabapentin, topiramate, and carbamazepine) produced a dose-dependent antinociceptive effect at different levels of pain in the rat formalin test [13].

10. Role of diacerein in many other disorders

In many studies, the additional potential effects of diacerein on many diseases and disorders have been discovered.

A recent clinical study in 2019, epidermolysis bullosa (EBS). A study evaluated the effect of 1% diacerein cream in the treatment of the patients of EBS, suggested that the topical diacerein is a potential drug to enhance the curing of skin wounds in EBS patients via the autoinflammatory activities and IL-1 downregulation [26].

Thyroid dysfunction was involved in the evaluation of diacerein activity. In a study of 21 days of treatment with diacerein (30 mg/kg/day), the concentration of the hormone of the thyroid gland and all other thyroid-related markers were corrected in carrageenan-induced thyroid dysfunction. It was suggesting that anti-inflammatory and antiperoxidative effects of diacerein in an animal model of inflammation were possibly facilitated via thyroid function alteration [90].

Additionally, it was apparent that diacerein (100 mg/kg/day), as an effective anti-inflammatory drug, can offer a therapeutic effect in the managing of periodontal disease. A potential therapeutic effect of the drug was due to its ability to decreasing inflammatory cytokine and regulating of signaling pathways, which ameliorate the inflammation-induced periodontal damage. Thus, the results indicated that diacerein could be of a pivotal role in controlling periodontal disease because of its established ability to diminish periodontal inflammation [28,29].

Furthermore, the ability of inflammatory blockage of diacerein (80 mg/kg) was associated with cardiac function, ventricular remodeling enhancement with decreased fibrosis in the left ventricular LV during 4 weeks of follow up with diacerein treatment [91] as well as inhibition of the development of intervertebral disc degeneration [30,92].

11. Conclusion

As reviewed here, different published researches with additional exploration of the clinical effect and possible mechanism of diacerein have convincingly reported the abilities of diacerein to exert various benefits. Depending on the pharmacological efficacy which mediated by anti-inflammatory, antioxidant and anti-apoptosis, diacerein shown to have a potential role in moderating the risk of many diseases such as kidney injury, diabetes mellites, cancer, ulcerative colitis, testicular toxicity, cervical hyperkeratosis, and pain, etc. In addition, the diacerein has a valuable addition in combination therapy as a synergetic agent leading support to the diseases; the linkage of these effects is shown in graphical abstract. Furthermore, many questions such as whether all of these potential indications of diacerein can be applied clinically and whether the molecular mechanisms and targets involved are enough, need to be elucidated by considerable essential clinical trials and experiments.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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